Official Title: A Phase III, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Satralizumab in Patients with Generalized Myasthenia Gravis

NCT Number: NCT04963270

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PROTOCOL

PROTOCOL TITLE:	**A PHASE III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY TO EVALUATE EFFICACY, SAFETY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF SATRALIZUMAB IN PATIENTS WITH GENERALIZED MYASTHENIA GRAVIS**
PROTOCOL NUMBER:	WN42636
VERSION NUMBER:	5
TEST PRODUCT:	Satralizumab (RO5333787)
STUDY PHASE	Phase III
REGULATORY AGENCY IDENTIFIER NUMBERS	IND Number: 151937 EudraCT Number: 2020-004436-21 *EU CT Number: 2023-507169-24-00* NCT Number: NCT04963270
CO-SPONSOR'S NAMES AND LEGAL REGISTERED ADDRESSES:	F. Hoffmann-La Roche Ltd Grenzacherstrasse 124 4070 Basel, Switzerland Chugai Pharmaceutical Co. Ltd.* 1-1 Nihonbashi-Muromachi 2-chome Chuo-ku, Tokyo 103-8324 Japan
APPROVAL:	See electronic signature and date stamp on the final page of this document.

CONFIDENTIAL

PROTOCOL HISTORY

Protocol		Associated Country-Specific Protocols		
Version	**Date Final**	**Country**	**Version**	**Date Final**
5	See electronic date stamp on the final page of this document	—	—	—
4	1 March 2023	France	5	30 March 2023
		China	4	30 March 2023
		The Netherlands	4	10 March 2023
3	10 November 2021	Germany	5	17 February 2023
		China	3	8 December 2021
		Germany	4	6 December 2021
		France	4	6 December 2021
2	16 February 2021	France	3	24 June 2021
		Germany	3	30 March 2021
		China	2	19 February 2021
1	1 February 2021	China	1	9 February 2021

PROTOCOL AMENDMENT, VERSION 5:
RATIONALE

Protocol WN42636 has primarily been amended to allow adolescent patients to enroll directly into the open-label extension (OLE) period, due to recruitment difficulties related to placebo use in the double-blind (DB) period. In response to the evolving gMG treatment landscape, the AChR-antibody seropositive population has been reduced from 192 to 160 participants (adults and adolescents) as the effect size (difference in mean change from baseline in Myasthenia Gravis Activities of Daily Living at Week 24 between satralizumab and placebo-treated arms) increased from 1.7 to 2. Consequently, the total sample size has been reduced from 240 to approximately 185 patients. Substantive changes to the protocol, along with a rationale for each change, are summarized below:

- The synopsis has been simplified to align with Clinical Trials Regulation (CTR) and other guidelines.
- A new section on adolescent enrollment (Section 3.1.3) has been added to reflect adolescent patient enrollment into the OLE period at study start, and the protocol has been revised throughout (Sections 3.1 [Figure 1], 3.1.4, 3.1.7, 3.2, 3.4.8, 4.2.1, 4.3.2, 4.5.2, 6,1, 6.4.8, and 6.5; Appendix 2).
- The pharmacokinetic interim analysis has been completed, and the text has been revised accordingly (Sections 3.1.1, 3.1.2,3.4.11, 4.3.2.1, 6.1, and 6.11.2).
- The protocol has been revised throughout to reflect the new sample size (Sections 3.1.7, 4.1, 6.1 and 9.6).
- Text regarding a China extended enrollment phase has been removed as the patient target has been reached. (Sections 3.1.5, 4.1, 4.1.1, 6.1, and 6.12).
- A section describing patient input into the study design has been added to align with CTR requirements (Section 3.1.8).
- A section describing duration of participation has been added to align with CTR requirements (Section 3.3).
- Studies listed in the Rationale for Secondary Outcome Measures have been updated to align with current study status (Section 3.4.6).
- Changes have been made to consolidate the protocols across EU countries to align with CTR requirements:

  The enrollment will be limited to adult patients (≥ 18 years old) for all participating sites in France (Sections 3.1.6, 3,4,2,3, and 4.1.1).

  An additional exclusionary criterion related to patients with Myasthenia Gravis Foundation of America (MGFA) Class IV at screening has been added for participants in France. The study will enroll patients with MGFA Class II or III at screening at participating sites in France (Sections 3.4.2.1, 4.1.1, and 4.1.2.1).

  The eligibility criterion in Section 4.1.1 has been consolidated to reflect that participating sites in the Netherlands and Germany use pre-existing positive

serologic test results ordered by a health care professional to support gMG diagnosis, instead of using antibody tests performed by the central laboratory during screening. Relevant changes have been made throughout the protocol (Sections 4.5.2, 4.5.3, and 4.5.6; Appendices 1, 2, and 3).

- The responsibilities of the investigator and the role of the Medical Monitor during study conduct have been clarified (Sections 4.2.2, 4.4 and 5.1.4.1).
- A comprehensive list of investigational medicinal products and auxiliary medicinal products has been added to align with CTR requirements in the European Economic Area (Section 4.3, 4.3.2.3 and Appendix 15). Additionally, non investigational medicinal products (NIMPs) language as per Clinical Trials Directive (CTD) has been removed from the protocol.
- Table 7 Recommended Dosage for Delayed or Missed Doses and after Rescue Therapy with Plasma Exchange has been amended to include recommendations for treatment interruptions (Section 4.3.2.2).
- Language has been added to indicate that sites can confirm that appropriate temperature conditions have been maintained during investigational medicinal product transit either by time monitoring (shipment arrival date and time) or temperature monitoring (Section 4.3.4).
- TSH has been removed from the central laboratory assessments (Section 4.5.6) to align with previously amended Section 4.1.2.4 and Appendix 1.
- Language has been added to clarify that adverse events associated with a special situation that also qualify as adverse events of special interest should be reported within 24 hours (Section 5.3.5.12).
- Language has been added to indicate that the Informed Consent Form will instruct female patients to inform the investigator if they become pregnant (Section 5.4.3.1).
- It has been made explicit that expedited safety reports are notified to EudraVigilance (Section 5.7).
- Text has been added to define the modified intent-to-treat population (mITT) (Sections 6, 6.1, and 6.4.1).
- The hierarchical gatekeeping has been updated to include mean change from baseline in Myasthenia Gravis Activities of Daily Living (MG-ADL) score in MuSK + and LRP4 + patients at Week 24 to align with the Statistical Analysis Plan (Section 6.4.3).
- The name of a Roche policy on data sharing has been corrected (Section 9.5).

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

PROTOCOL AMENDMENT ACCEPTANCE FORM

PROTOCOL TITLE:	**A PHASE III RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY TO EVALUATE EFFICACY, SAFETY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF SATRALIZUMAB IN PATIENTS WITH GENERALIZED MYASTHENIA GRAVIS**
PROTOCOL NUMBER:	WN42636
VERSION NUMBER:	5
TEST PRODUCT:	Satralizumab (RO5333787)
CO-SPONSORS:	F. Hoffmann-La Roche Ltd Chugai Pharmaceutical Co. Ltd.*

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by your local study monitor.

PROTOCOL SYNOPSIS

PROTOCOL TITLE:	**A PHASE III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY TO EVALUATE EFFICACY, SAFETY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF SATRALIZUMAB IN PATIENTS WITH GENERALIZED MYASTHENIA GRAVIS**
REGULATORY AGENCY IDENTIFIERS:	IND Number: 1..... EudraCT Number: 2020-004436-21 *EU CT Number: 2023-507169-24-00* NCT Number: NCT0496327

STUDY RATIONALE

The purpose of this study is to evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of satralizumab compared with placebo as add-on therapy to standard of care (SOC) for the treatment of generalized myasthenia gravis (gMG), which is a chronic autoimmune condition that has substantial impact on day-to-day functioning of patients. In addition, the study will assess the long-term safety and efficacy of satralizumab during the open-label extension (OLE) period.

OBJECTIVES AND ENDPOINTS

Table 1 Objectives and Endpoints during the Double-Blind Period

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of satralizumab versus placebo on function in daily life in the AChR+ population	• Mean change from baseline in total MG-ADL score at Week 24

AChR = acetylcholine receptor; AChR+ = AChR-antibody seropositive (patients/population); ADA = anti-drug antibody; AUC = area under the concentration–time curve; CL/F = apparent clearance; C_{trough} = trough concentration; gMG = generalized myasthenia gravis; IL-6 = interleukin-6; MG-ADL = Myasthenia Gravis Activities of Daily Living; MGC = Myasthenia Gravis Composite; MG-QOL 15r = Myasthenia Gravis Quality of Life 15 Scale (revised); NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; Neuro–QoL = Quality of Life in Neurological Disorders; OP = overall population; PK = pharmacokinetic; QMG = Quantitative Myasthenia Gravis; QoL = quality of life; sIL-6R = soluble interleukin-6 receptor; V/F = apparent volume of distribution.

[a] Patients who receive rescue therapy will be considered non-responders

Table 1 Objectives and Endpoints during the Double-Blind Period (cont.)

Secondary Efficacy Objectives	Corresponding Endpoints
• To evaluate the efficacy of satralizumab versus placebo on function in daily life in the OP	• Mean change from baseline in total MG-ADL score at Week 24
• To evaluate the efficacy of satralizumab versus placebo in the AChR+ population and OP on:	
– Function in daily life	• Percentage of patients with a ≥2-point reduction from baseline in total MG-ADL score at Week 24[a]
– QMG, QoL, and Fatigue	• Mean change from baseline in QMG score, MG-QOL 15r total score and Neuro–QoL Fatigue Subscale total score at Week 24 • Percentage of patients with a ≥3-point reduction from baseline in QMG score at Week 24[a]
– Clinical status	• Mean change from baseline in total MGC score at Week 24 • Percentage of patients with a ≥3-point reduction from baseline in total MGC score at Week 24 [a]
– Disease severity	• Proportion of patients: – Who have achieved minimal disease manifestation (total MG-ADL score of 0 or 1) at Week 24 [a] – With at least one gMG-related exacerbation between baseline and Week 24 – Receiving rescue therapy between baseline and Week 24 • Annualized rate of gMG-related exacerbations
• To evaluate the durability of the efficacy of satralizumab versus placebo in the AChR+ population and the OP	• Duration (average number of consecutive months) of meaningful improvement, defined as ≥2-point reduction from baseline in total MG-ADL score [a]

AChR = acetylcholine receptor; AChR+ = AChR-antibody seropositive (patients/population); ADA = anti-drug antibody; AUC = area under the concentration–time curve; CL/F = apparent clearance; C_{trough} = trough concentration; gMG = generalized myasthenia gravis; IL-6 = interleukin-6; MG-ADL = Myasthenia Gravis Activities of Daily Living; MGC = Myasthenia Gravis Composite; MG-QOL 15r = Myasthenia Gravis Quality of Life 15 Scale (revised); NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; Neuro–QoL = Quality of Life in Neurological Disorders; OP = overall population; PK = pharmacokinetic; QMG = Quantitative Myasthenia Gravis; QoL = quality of life; sIL-6R = soluble interleukin-6 receptor; V/F = apparent volume of distribution.

[a] Patients who receive rescue therapy will be considered non-responders

Table 1 Objectives and Endpoints during the Double-Blind Period (cont.)

Safety Objective	Corresponding Endpoints
• To evaluate the safety of satralizumab versus placebo	• Incidence and severity of adverse events, with severity determined according to NCI CTCAE v5.0 grading • Change from baseline in targeted vital signs, ECG results, physical examination findings, targeted clinical laboratory test results, and suicidality
Pharmacokinetic Objective	**Corresponding Endpoints**
• To investigate the pharmacokinetics of satralizumab by evaluating plasma exposure over 24 weeks	• Serum concentrations of satralizumab (mean and SD of C_{trough}) at specified timepoints • Estimates of primary PK parameters (e.g., CL/F and V/F) and secondary PK parameters (e.g., AUC) derived using population–PK modeling
Immunogenicity Objective	**Corresponding Endpoint**
• To evaluate the immune response to satralizumab	• Prevalence of ADAs at baseline and incidence of ADAs during the study

AChR = acetylcholine receptor; AChR+ = AChR-antibody seropositive (patients/population); ADA = anti-drug antibody; AUC = area under the concentration–time curve; CL/F = apparent clearance; C_{trough} = trough concentration; gMG = generalized myasthenia gravis; IL-6 = interleukin-6; MG-ADL = Myasthenia Gravis Activities of Daily Living; MGC = Myasthenia Gravis Composite; MG-QOL 15r = Myasthenia Gravis Quality of Life 15 Scale (revised); NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; Neuro–QoL = Quality of Life in Neurological Disorders; OP = overall population; PK = pharmacokinetic; QMG = Quantitative Myasthenia Gravis; QoL = quality of life; sIL-6R = soluble interleukin-6 receptor; V/F = apparent volume of distribution.

[a] Patients who receive rescue therapy will be considered non-responders

Table 2 Objectives and Endpoints during the Open-Label Period

Safety Objective	Corresponding Endpoints
• To evaluate the long-term safety and tolerability of satralizumab	• Incidence and severity of adverse events, with severity determined according to NCI CTCAE v5.0 grading • Change from baseline in targeted vital signs, ECG results, physical examination findings, targeted clinical laboratory test results, and suicidality
Efficacy Objectives	**Corresponding Endpoints**
• To assess the efficacy of satralizumab in the AChR+ population and OP	• Mean change from active treatment baseline in: – MG-ADL total score – QMG score – MGC score – MG-QOL 15r score • Percentage of responders [a] based on: – ≥2-point reduction in total MG-ADL score or – ≥3-point reduction in QMG score or – ≥3-point reduction in total MGC score • Proportion of time and duration that patients show a meaningful improvement, defined as a ≥2-point reduction from active treatment baseline in total MG-ADL score • Number and severity of gMG-related exacerbations
• To assess the effect of satralizumab on steroid/IST/AChEI dose modification in the AChR+ population and OP	• The proportion of patients who maintain clinical response without increase in symptomatic medication dose and are able to reduce corticosteroid dose or withdraw from corticosteroid or IST during the OLE

AChEI = acetylcholinesterase inhibitor; AChR = acetylcholine receptor; AChR+ = AChR-antibody seropositive (patients/population); ADA = anti-drug antibody; AUC = area under the concentration–time curve; CL/F = apparent clearance; C_{trough} = trough concentration; IL-6 = interleukin-6; IST = immunosuppressant; MG-ADL = Myasthenia Gravis Activities of Daily Living; MG-QOL 15r = Myasthenia Gravis Quality of Life 15 Scale (revised); NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; OLE = open-label extension; OP = overall population; PD = pharmacodynamic; PK = pharmacokinetic; QMG = Quantitative Myasthenia Gravis; QoL = quality of life; sIL-6R = soluble interleukin-6 receptor; V/F = apparent volume of distribution.

Table 2 Objectives and Endpoints during the Open-Label Period (cont.)

Pharmacokinetic Objective	Corresponding Endpoints
• To investigate the pharmacokinetics of satralizumab by evaluating plasma exposure in the OLE	• Serum concentrations of satralizumab (mean and SD of C_{trough}) • Estimates of primary PK parameters (e.g., CL/F and V/F) and secondary PK parameters (e.g., AUC) derived using population–PK modeling
Immunogenicity Objective	Corresponding Endpoint
• To evaluate the immune response to satralizumab	• Prevalence of ADAs at baseline and incidence of ADAs during the OLE
Pharmacodynamic Objective	Corresponding Endpoint
• To confirm target engagement and pathway inhibition in response to satralizumab	• Absolute values and change from baseline in serum levels of PD biomarkers IL-6 and sIL-6R

AChEI = acetylcholinesterase inhibitor; AChR = acetylcholine receptor; AChR+ = AChR-antibody seropositive (patients/population); ADA = anti-drug antibody; AUC = area under the concentration–time curve; CL/F = apparent clearance; C_{trough} = trough concentration; IL-6 = interleukin-6; IST = immunosuppressant; MG-ADL = Myasthenia Gravis Activities of Daily Living; MG-QOL 15r = Myasthenia Gravis Quality of Life 15 Scale (revised); NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; OLE = open-label extension; OP = overall population; PD = pharmacodynamic; PK = pharmacokinetic; QMG = Quantitative Myasthenia Gravis; QoL = quality of life; sIL-6R = soluble interleukin-6 receptor; V/F = apparent volume of distribution.

OVERALL DESIGN AND STUDY POPULATION

This Phase III, randomized, double-blind (DB), placebo-controlled, multicenter study is designed to evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of satralizumab compared with placebo as add-on therapy to SOC for the treatment of gMG. The study will include a 28-day screening period, a 24-week DB treatment period, and approximately 2-year OLE period after the last patient initiates open-label treatment. *As of global protocol Version 5, adolescent patients enrolled in the study will directly enter the OLE period after completion of the screening period.*

Several key aspects of the study design and study population are summarized in the table below.

Phase:	Phase III	**Population Type:**	Adult and pediatric patients
Control Method:	Placebo (DB period) and none (OLE period)	**Population Diagnosis or Condition:**	gMG
Interventional Model:	Parallel (DB period) and single group (OLE period)	**Population Age:**	Adults ≥ 18 years [a] and adolescents ≥ 12 years to < 18 years
Test Product{s}:	Satralizumab	**Site Distribution:**	Multi-site and multi-region
Active Comparator:	Not applicable	**Study Treatment Assignment Method:**	Randomization and stratification
Number of Arms:	2	**Number of Participants to Be Enrolled:**	Approximately *185*

DB = double-blind; gMG = generalized myasthenia gravis; OLE = open-label extension

[a] *Only adult patients aged ≥ 18 years old will be included at participating sites in France*

STUDY TREATMENT

Weight-tiered dosing via SC injection will be used in this study.

Table 3 Dosing Regimen: Double-Blind Period

Body Weight at Baseline [a]	Dose and Regimen
≤ 100 kg	120 mg satralizumab/placebo administered at Weeks 0, 2, 4 (loading doses), and maintenance doses Q4W thereafter as a SC injection
> 100 kg	180 mg satralizumab/placebo administered at Weeks 0, 2, 4 (loading doses), and maintenance doses Q4W thereafter as a SC injection

SC = subcutaneous, Q4W = every 4 weeks.

[a] Recommendations in case of changes in body weight in an individual patient would result in a different dosing band are given in the protocol.

During the OLE period, all patients will receive open-label treatment with 120 mg or 180 mg satralizumab, as determined based on body weight (see above). *Adult and adolescent* patients who receive placebo during the DB period will receive satralizumab SC loading doses at Weeks 0, 2, and 4 in the OLE, followed by maintenance doses every 4 weeks (Q4W) thereafter during the OLE period. *Adult and adolescent* patients who receive active treatment during the DB period will continue receiving satralizumab SC Q4W during the OLE period, but will receive an additional placebo SC injection at Week 2 to maintain blinding to DB treatment assignment.

Adolescent patients who first enter the study in the OLE period will receive satralizumab SC loading doses at Week 0, 2, and 4 in the OLE, followed by maintenance doses Q4W thereafter and will remain on stable background therapy until Week 24 of the OLE.

Information on delayed or missed doses, as well as background therapy and rescue medication, can be found in the protocol.

DURATION OF PARTICIPATION

The total duration of study participation for each individual enrolled in the DB period is expected to be approximately 2.5–4 years, depending on when the participant enters the OLE and the duration of time the participant spends in this period.

The total duration of study participation for adolescent patients enrolled directly in the OLE period is approximately 2 –3.5 years, according to the estimated recruitment timelines.

COMMITTEES

Independent Committees:	Independent Data Monitoring Committee
Other Committees:	Not applicable

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AChE	acetylcholinesterase
AChEI	acetylcholinesterase inhibitors
AChR	acetylcholine receptor
AChR+	AChR-antibody seropositive (patients/population)
ADA	anti-drug antibody
AQP4	Aquaporin-4
AUC	area under the concentration–time curve;
AxMP	*auxiliary medicinal product*
CL	total clearance of drug
CL/F	apparent clearance
ClinRO	clinician-reported outcome
C_{max}	maximum concentration observed
COVID-19	coronavirus disease 2019
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	trough concentration
$C_{tr,ss}$	trough concentration at steady state
C-SSRS	Columbia Suicide Severity Scale
CSR	Clinical Study Report
DB	double-blind;
EAMG	experimental autoimmune myasthenia gravis
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
EEA	*European Economic Area*
EFF	extended finger flange
EOT	end of treatment
FDA	Food and Drug Administration
GI	gastrointestinal
gMG	generalized myasthenia gravis
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCP	health care professional
HIPAA	Health Insurance Portability and Accountability Act

Abbreviation	Definition
HRQOL	health-related quality-of-life
HV	healthy volunteer
ICC	intra-class correlation coefficient
ICH	International Council for Harmonisation
iDCC	independent Data Coordinating Center
iDMC	independent Data Monitoring Committee
IFN-γ	interferon-γ
IL-6	interleukin-6
IL-6R	interleukin-6 receptor
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IST	immunosuppressant
IVIg	intravenous immunoglobulin
IxRS	interactive voice or web-based response system
JMG	juvenile myasthenia gravis
LPLV	last patient, last visit
LRP4	low-density lipoprotein receptor–related protein 4
MCID	minimum clinically important difference
MG	Myasthenia gravis
MG-ADL	Myasthenia Gravis Activities of Daily Living
MGC	Myasthenia Gravis Composite
MGFA	Myasthenia Gravis Foundation of America
MG-QOL 15r	Myasthenia Gravis Quality of Life 15 Scale (revised)
mIL-6R	membrane-bound IL-6R
mITT	modified intent-to-treat (population)
MM	minimal manifestations
MN	mobile nurse
MuSK	muscle-specific kinase
NCI	National Cancer Institute
Neuro–QoL	Quality of Life in Neurological Disorders
NGS	next-generation sequencing
NMJ	neuromuscular junction
NMOSD	neuromyelitis optica spectrum disorder
NSD	needle safety device
NSDCR	not study drug or condition related
OCS	oral corticosteroids

Abbreviation	Definition
OLE	open-label extension
OP	overall population
PBMCs	peripheral blood mononuclear cells
PD	pharmacodynamic
PE	plasma exchange
PFS	prefilled syringe
PK	pharmacokinetic
pop PK	population PK
PRO	patient-reported outcome
PY	patient years
QMG	Quantitative Myasthenia Gravis score
QoL	quality of life
QTcF	QT interval corrected through use of Fridericia's formula
Q4W	every 4 weeks
RA	rheumatoid arthritis
RBR	Research Biosample Repository
RO	receptor occupancy
ROC	receiver operating curves
$RO_{tr,ss}$	trough receptor occupancy at steady-state
SAP	Statistical Analysis Plan
SDCR	study drug or condition related
SFU	safety follow-up
sIL-6R	soluble interleukin-6 receptor
SJS	Stevens-Johnson Syndrome
SOC	standard of care
TB	tuberculosis
Treg	regulatory T cells
Th17	T-helper 17
ULN	upper limit of normal
VAS	visual analogue scale
WES	whole exome sequencing
WGS	whole genome sequencing

1. BACKGROUND

1.1 BACKGROUND ON MYASTHENIA GRAVIS

Myasthenia gravis (MG) is a rare chronic autoimmune disease that affects the postsynaptic membrane at the neuromuscular junction (NMJ). The hallmark of the disorder is a fluctuating degree and variable combination of fatigable weakness in ocular, facial, bulbar (oropharyngeal), respiratory, trunk (axial), and limb muscles. Bulbar weakness results in difficulties with chewing, swallowing (dysphagia), and talking (dysarthria). Fatigability is characterized by worsening of the weakness with exercise and repetitive muscle use; as a result, it is typically most pronounced in the evening.

There are two clinical forms of MG: ocular MG, present in about 15% of patients, and generalized MG (gMG), affecting about 85% of patients (Gilhus et al. 2019). In ocular MG, the weakness is limited to the eyelids and extraocular muscles resulting in drooping of the eyelid (ptosis) and double vision (diplopia), respectively. In gMG, the weakness commonly affects ocular muscles in combination with other muscle groups.

More than 50% of patients with MG experience ocular manifestations as their initial symptoms. In contrast, approximately 15% of patients experience facial and bulbar weakness as their initial manifestations. Less than 5% of patients present with proximal limb weakness alone. Less common presentations include isolated neck weakness, isolated respiratory muscle weakness, and distal limb weakness (Gilhus et al. 2019).

Myasthenia gravis has a variable course. The disease usually peaks within a few years from disease onset. More than half of the patients who present with ocular manifestations at disease onset will develop generalized disease within the first 2 years. Many of the patients who have no ocular manifestations at disease onset develop ptosis or diplopia at some point in the course of the disease. Disease worsening (clinical exacerbations) can be triggered by infections, surgery, and certain medications. About 15% of patients experience myasthenic crisis, characterized by weakness of the diaphragm and accessory breathing muscles resulting in respiratory failure. Myasthenic crisis is a neurologic emergency that is managed in the intensive care setting with ventilatory support and fast-acting therapies. MG is not considered a progressive disease as permanent muscle damage and resulting irreversible disability rarely occurs.

The listed MG symptoms substantially influence the daily life of the patients. Ptosis has significant impact on the quality of life (QoL) not only because it impairs vision but also because it makes the affected individual self-conscious and thus results in social withdrawal (Richards et al. 2014). Diplopia, fatigue, and weakness hinder the affected individual from completing basic daily tasks, including taking care of their hygiene (Basta et al. 2012). Considering the interferences of daily functioning due to the symptoms of MG, heightened depression and lowered QoL are common (Leonardi et al. 2010; Yang et al. 2016; Koopman et al. 2016).

Prevalence and incidence of MG ranges substantially across the literature according to study methodology, study period, and the sociodemographic distribution of the study population. The majority of studies in the literature report estimated prevalence of MG as 15–240 cases per million individuals globally, although some regional European studies report a prevalence as high as 329–649 cases per million individuals (Carr et al. 2010; Montomoli et al. 2012; Leoni et al. 2014; Aragonès et al. 2017).

As with prevalence, the reported cumulative incidence has increased over time, likely due to improvements in diagnosis, more widespread antibody testing, and physician awareness. Studies published during 1950–1994 report an incidence of 2–15 per million individuals, while more recent studies report an increased incidence of 9–104 per million individuals (Phillips and Torner 1996; Kumar et al. 2020).

MG is caused by autoantibodies that bind to acetylcholine receptors (AChRs) or to other functionally related molecules in the postsynaptic membrane at the NMJ, such as muscle-specific kinase (MuSK) or low-density lipoprotein receptor–related protein 4 (LRP4). Patients with positive AChR, MuSK, or LRP4 autoantibodies have seropositive MG. Patients in whom currently commercially available tests did not detect presence of the three types of autoantibodies are considered seronegative. Approximately 85% of patients with gMG test positive for AChR autoantibodies (AChR+ MG), 7%–8% for MuSK autoantibodies (MuSK+ MG), and 1%–3% for LRP4 autoantibodies (LRP4+ MG), whereas about 6% of patients are seronegative. Autoantibody production in MG is a T-cell–dependent process, and the thymus is thought to play an important role in the dysregulation of self-tolerance and ultimately MG pathogenesis. The majority of patients with AChR antibody–seropositive (AChR+) MG have thymic abnormalities: hyperplasia in 60%–70% and thymoma in 10%–12% of patients.

MG is classified into subgroups according to clinical manifestations, age at onset, the presence of autoantibody pattern, and thymus pathology (see Table 1) (Gilhus and Verschuuren 2015; Gilhus 2016). Ocular MG and LRP4+ MG tend to be milder, whereas MuSK+ MG and probably thymoma-associated MG tend to be more severe (Andersen et al. 2016).

Table 1 Classification of Myasthenia Gravis Subgroups

Subgroup	Autoantibody	Age at Onset (years)	Thymus Abnormalities
Early-onset MG [a]	AChR	< 50	Hyperplasia common
Late-onset MG	AChR	> 50	Atrophy common
Thymoma-associated MG	AChR	Any	Type AB and B thymoma
MuSK MG	MuSK	Any	Normal
LRP4 MG	LRP4	Any	Normal
Seronegative MG	None detected	Any	Variable
Ocular MG [b]	AChR, MuSK, LRP4, or none	Any	Variable

AChR = acetylcholine receptor; LRP4 = low-density lipoprotein receptor–related protein 4; MG = myasthenia gravis; MuSK = muscle-specific kinase.

[a] Juvenile MG is not considered a separate subgroup and is part of early-onset MG. All patients at one time point can belong only to one subgroup.

[b] Ocular MG includes the patients with ocular symptoms only and no clinical weakness in other muscles.

The age at onset of AChR MG often has a bimodal pattern, with a lower peak observed at around 30 years of age and a higher peak at 70–80 years of age (Heldal et al. 2009; Carr et al. 2010; Andersen et al. 2010). The incidence peak in young adults is mainly attributed to women, whereas late-onset MG is slightly more frequent in men (Carr et al. 2010; Gilhus and Verschuuren 2015).

1.2 JUVENILE MYASTHENIA GRAVIS

Juvenile, or childhood, MG (JMG), defined by onset before the age of 18 years (O'Connell 2020) shares aspects of pathophysiology and most of the clinical features of adult early-onset MG (Gilhus et al. 2019). JMG is distinguished from genetic, non-autoimmune forms of neuromuscular transmission defect, the so-called congenital myasthenic syndromes.

The juvenile-onset and adult-onset MG differ with respect to epidemiology, frequency of ocular and generalized MG forms, prognosis, and therapeutic approaches.

A range of 12–80% of patients with JMG have been reported to have gMG (Chung et al. 2003; Kalb et al. 2002; Popperud et al. 2017), which is below the estimated frequency of 85% in adults. gMG is relatively uncommon in prepubertal children, regardless of race (Chung et al, 2003, O'Connell et al. 2020).

The pathophysiology of MG in pediatric patients is highly similar to that of adults. JMG is also caused by autoantibodies that bind to AChR or to other functionally relevant molecules in the postsynaptic membrane at the NMJ, such as MuSK or LRP4.

However the percentage of patients seropositive for these molecules differ from adult-onset MG: majority of patients (90%) are AChR+, < 8% are MuSK+, and < 2% are LRP4+, whereas about 10%–30% of patients are seronegative (Finnis and Jayawant 2011; Takahashi et al. 2012; VanderPluym et al. 2013; Baraud 2018; Vecchio et al. 2020).

Diagnosis of JMG is established using the same evaluations and procedures as in adult MG.

1.3 CURRENT TREATMENT AND UNMET MEDICAL NEED

The goal of therapy in gMG is to induce pharmacological remission, complete stable remission, or minimal manifestations (MM), while minimizing side effects from medications (Jaretzki et al. 2000). The Myasthenia Gravis Foundation of America (MGFA) post-intervention status defines MM as a patient who has no symptoms or functional limitations from gMG but has some weakness on examination of some muscles. In October 2013, the MGFA appointed a Task Force, a panel of 15 international experts, who developed consensus-based guidance for the management of MG, which was published in 2016 (Sanders et al).

In contrast to adult MG there are no internationally accepted standards of care for JMG, and prospective randomized controlled data to evaluate treatment outcomes and efficacy have been difficult to collect. Most of the current practice on JMG diagnosis and treatment is extrapolated from adult trials and experience.

There are three types of primary therapies used to treat gMG:

- Symptomatic treatment using acetylcholinesterase (AChE) inhibitors (AChEIs; anti-cholinesterases)
- Immunosuppressive and immunomodulatory therapies
- Thymectomy

Symptomatic treatment using AChEI increases the amount of acetylcholine available at the NMJ. Given its oral route of administration, pyridostigmine bromide is the preferred AChEI, and is usually the first-line medication in patients with gMG, including those with JMG. All subgroups of patients with gMG, with the exception of patients with MuSK+ gMG, respond to AChEIs but with inter-individual variability in the degree of weakness relief, optimal dosage, and tolerability (Finnis and Jayawant et al. 2011; O'Connell et al. 2020). Muscle strength can be restored to normal levels over long periods in only a few patients with mild disease.

Chronic immunosuppressive therapies (glucocorticoids and non-steroidal immunosuppressive agents) target the underlying immune dysregulation. Patients with symptoms that exert functional impairment or reduce QoL when on maximum tolerated AChEI treatment should receive immunotherapy. Commonly used immunosuppressive therapies include oral corticosteroids (OCSs), antimetabolites (such as azathioprine,

mycophenolate mofetil, or methotrexate) and calcineurin inhibitors (such as cyclosporine and tacrolimus). The time of onset of clinical effect of each of these therapies for gMG varies considerably ranging from a few weeks for OCSs to approximately 2–12 months for mycophenolate mofetil and azathioprine (Sanders et al. 2016). The time of onset plays a large role, in addition to the pace and severity of the disease, in choosing the appropriate therapy for a given patient.

OCSs are first-line immunotherapy drugs for adult-onset and juvenile MG (O'Connell et al. 2020); in children, they are used cautiously, at the lowest possible dose because of growth retardation and other chronic systemic side effects, including weight gain, cushingoid features, hyperglycemia, hypertension, cataracts, glaucoma, behavioral changes, and susceptibility to infection.

Conventional steroid-sparing immunosuppressive agents are used on a limited basis in children because of the long-term risk of malignancy and teratogenicity (Munot et al. 2020); methotrexate, cyclosporine and cyclophosphamide are reserved only for refractory cases (see Section 4.5.3 for definition).

Patients with insufficient response, further disease worsening, or intolerance to the above medications may receive treatment with chronic IV immunoglobulin (IVIg), plasma exchange (PE), B-cell depletion with rituximab, or terminal complement activation inhibition with eculizumab (Soliris® U.S. Package Insert; Sanders et al. 2016). In single-arm study reports, rituximab was effective but with varying response rates (Anderson et al. 2016; Tandan et al. 2017; Robeson et al. 2017). Furthermore, in a Phase II trial in patients with AChR gMG (NCT02110706) rituximab was safe and well tolerated, but the study did not reach the primary endpoint of a 75% reduction in glucocorticoid levels. The use of rituximab in refractory JMG is sparsely documented (Zingariello et al. 2020; Barraud et al. 2018). Many of the therapies used in MG, including rituximab, are used off-label.

Therapeutic PE and IVIg are rapid but short-acting immunomodulating treatments. As such, they are typically used in patients with acute severe gMG when a rapid response is crucial, and are the mainstay of management of myasthenic crisis. As their effect is short-lived (4–12 weeks), maintenance immunotherapy is usually needed. They may be used as chronic, maintenance therapy in patients with refractory gMG (see Section 4.5.3 for definition) or in patients for whom immunosuppressive agents are relatively contraindicated, such as the pediatric population.

Thymectomy is indicated for patients with thymoma if resection is feasible and in many other AChR antibody–positive patients with non-thymomatous gMG who are 18–65 years old. In patients with a non-neoplastic thymus, thymectomy for the improvement of gMG has been performed for several decades, and is supported by extensive evidence on the pathogenetic role of the thymus in AChR + gMG and by a large number of studies showing a higher remission rate after thymectomy (Skeie et

al. 2010; Wolfe et al. 2016; Gronseth et al. 2020). The role and timing of thymectomy is still not well established or standardized in children. It is usually considered as a therapeutic option in AChR+ gMG when the response to pyridostigmine and ISTs is incomplete or to avoid the long-term side effects of ISTs, especially corticosteroids. Thymectomy does not have an effect in MuSK gMG and has not been systematically examined in patients with gMG who have no detectable antibodies. Thymectomy does not cure gMG, and the long-term effect on antibody concentrations, T-cell subsets, and immune responses is very modest.

The majority of treated patients achieve a relatively stable condition allowing them to perform daily tasks (Andersen et al. 2016). However, only a few patients achieve remission, i.e., have no symptoms or signs of gMG and no evidence of weakness of any muscle on neurological examination. Even if fully functional, many patients experience side effects of the above listed treatments for gMG (Bacci et al. 2019). While children tend to exhibit higher rates of spontaneous or pharmacologic remission than adults, the frequency of refractory MG in pediatric population is unknown. OCSs, the most commonly used and fast-acting medications, result in a plethora of adverse effects that almost universally limit patients' QoL. Steroid-sparing agents are suboptimal alternatives because of their non-specific immunosuppressive profile, onset of action that may be delayed by more than 6 months, and significant long-term side effects, including malignancies. IVIg and therapeutic PE are associated with considerable logistical challenges. Overall, the unmet need in gMG remains high for disease-specific, more effective, safer, and relatively convenient treatments.

1.4 BACKGROUND ON SATRALIZUMAB

Satralizumab (RO5333787) is a humanized anti–interleukin-6 receptor (IL-6R) IgG2 monoclonal antibody that was constructed by modifying the amino acid sequence of tocilizumab to prolong its plasma drug-elimination half-life. In addition, satralizumab has the following distinguishing characteristics: pH-dependent binding to its antigen (IL-6R) (Igawa et al. 2010a), decreased antibody molecule isoelectric point (Igawa et al. 2010b), and stronger binding to neonatal Fc receptor (Petkova et al. 2006). Moreover, its Fc region has been modified to minimize antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity effector activity.

Satralizumab maintains pharmacological effects of IL-6R blockade using a 4-week dosing frequency by SC injection due to its prolonged plasma drug-elimination half-life. Satralizumab specifically targets the human IL-6R, preventing interleukin (IL)-6 from binding to the membrane-bound and soluble IL-6R (mIL-6R and sIL-6R respectively), thereby inhibiting IL-6 signaling.

The clinical pharmacology, safety, and efficacy of satralizumab has been characterized in four clinical trials: a single ascending dose (SA-001JP) trial in healthy subjects (both Japanese and Caucasian), a multiple ascending dose (SA-105JP) trial in patients with

rheumatoid arthritis (RA), and two Phase III clinical studies in patients with neuromyelitis optica spectrum disorder (NMOSD; BN40898 [SA-307JG] and BN40900 [SA-309JG).

Study BN40900 was a randomized (2:1 ratio), placebo-controlled trial in 95 patients without concurrent immunosuppressant (IST) therapy, and Study BN40898 was a randomized (1:1 ratio), placebo-controlled trial in 83 patients (76 adults and 7 adolescents, aged 12 to $\leq$ 17 years) using concurrent IST. All patients in Study BN40898 were receiving either concurrent azathioprine (34.9%), OCS (44.6%), or mycophenolate mofetil (14.5%) during the trial. Five adolescent patients received a combination of azathioprine or mycophenolate mofetil with corticosteroids. Meaningful and comparable efficacy based on relative risk of experiencing relapse was demonstrated in both Phase III studies in aquaporin-4 (AQP4) IgG–seropositive patients. The relative risk of experiencing an adjudicated relapse in AQP4-IgG–seropositive patients was reduced by 79% in Study BN40898 (N = 55) and by 74% in Study BN40900 (N = 64). Satralizumab 120 mg every 4 weeks (Q4W) given as monotherapy or in combination with IST was safe and well tolerated by patients with NMOSD.

Results from the Phase III clinical Studies BN40898 and BN40900 confirmed the adequacy of the selected dosing regimen (doses of 120 mg administered at Weeks 0, 2, and 4 followed by 120 mg Q4W). At this dose, the effective drug-elimination half-life is approximately 30 days based on data pooled between the two studies, supporting the recommended maintenance dosing interval of Q4W. Robust sIL-6R stabilization and increases in IL-6 levels were seen, indicative of target engagement. The median predicted occupancy at the sIL-6R and mIL-6R in patients with NMOSD was maintained at $>$ 95% throughout the dose interval, and for the entire duration of therapy (Week 180 and Week 204 in Studies BN40898 and BN40900, respectively).

In Studies BN40898 and BN40900, anti-drug antibodies (ADAs) were observed in 41% and 71% of patients receiving satralizumab in the double-blind (DB) period, respectively. Apparent correlations between ADA development and higher body weight and lower exposure, were not reflected in clinical outcomes. Meaningful and comparable efficacy was demonstrated in all exposure subgroups and in all body weight groups.

During the Phase III studies BN40898 and BN40900 in NMOSD, satralizumab demonstrated a favorable safety profile. During the DB period, 63 patients were exposed to satralizumab monotherapy and 41 patients were exposed to satralizumab in combination with IST (please refer to the Satralizumab Investigator's Brochure for further details). In the DB period, patient median exposure to satralizumab was approximately two years in both studies. The median exposure to placebo was approximately one year.

Overall, satralizumab was well tolerated by patients with NMOSD. The safety profile of satralizumab in combination with OCS (15 mg of prednisolone equivalent per day), azathioprine or mycophenolate mofetil was comparable to satralizumab monotherapy.

The PK and safety profiles of satralizumab in adolescent patients was comparable to those in adult patients with NMOSD.

The most frequently reported adverse drug reactions were headache, arthralgia and injection reactions. The majority of adverse events were of mild or moderate severity and resolved without changes to the study drug. Injection reactions were reported in 12.5% of the patients treated with satralizumab (monotherapy or in combination with IST) and were predominantly of mild to moderate severity. The incidence rate of infections was not higher in the satralizumab group compared to the placebo group in both the monotherapy study (satralizumab: 99.8 events/100 patient years (PY) [95% CI: 82.4 to 119.8]; placebo: 162.6 events/100 PY [95% CI: 125.8 to 206.9]) and in the add-on study (satralizumab + IST: 132.5 events/100 PY [95% CI: 108.2 to 160.5]; placebo + IST: 149.6 events/100 PY [95% CI: 120.1 to 184.1].

Laboratory abnormalities including neutropenia, thrombocytopenia, elevations in liver enzymes, and lipid elevations have been reported in patients treated with satralizumab.

Please refer to the Satralizumab Investigator's Brochure for details on nonclinical and clinical studies

1.5 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

Satralizumab is being developed for treatment of gMG, which is a chronic autoimmune condition that has substantial impact on day-to-day functioning of patients.

1.5.1 Rationale for IL-6 Inhibition as a Therapeutic Mode of Action in Generalized Myasthenia Gravis

IL-6 is a pleiotropic inflammatory cytokine produced by T-cells, monocytes, macrophages, and fibroblasts that mediates various functions through the IL-6R (Kishimoto 2010; Tanaka and Kishimoto 2012). It acts as a regulator of B- and T-cell functions, induces the differentiation of activated B-cells into antibody-producing plasma cells and the production of complement components. Given the pathological relevance of autoantibodies, pro-inflammatory T-cell activity, and complement activation in gMG, IL-6 inhibition through satralizumab is expected to dampen immune mechanisms that underlie the clinical phenotype of gMG.

A study in IL-6 knockout mice investigated the role of IL-6 in experimental autoimmune myasthenia gravis (EAMG) (Deng et al. 2002). IL-6 gene knockout (IL-6 $^{-/-}$) mice in the C57BL/6 background were immunized with Torpedo californica AChR and evaluated for EAMG. Only 25% of AChR-immunized IL-6 $^{-/-}$ mice developed clinical EAMG compared with 83% of C57BL/6 (wild type) mice. The AChR-specific lymphocyte proliferative response, interferon-γ (IFN-γ), and IL-10 production were suppressed in AChR-immunized IL-6 $^{-/-}$ mice. EAMG resistance in IL-6 $^{-/-}$ mice was associated with a significant reduction in germinal center formation and decreased serum complement C3

levels. These data provide direct genetic evidence for a key role of IL-6 in the autoimmune response to AChR and in EAMG pathogenesis.

A study in EAMG-induced and healthy control rats assessed if the equilibrium between suppressive regulatory T cells (Treg) and pathogenic T-helper (Th) 17 cells is perturbed in the disease and showed that Th17 cell-related genes are upregulated and Treg-related genes are downregulated in EAMG. The shift in favor of Th17 cells in EAMG could be reversed by antibodies to IL-6 (Aricha et al. 2011). Administration of anti–IL-6 antibodies cross-reactive to rat IL-6 to myasthenic rats suppressed EAMG when treatment was started during the acute or the chronic phase of disease. Suppression of EAMG by anti–IL-6 antibodies was accompanied by a decrease in the overall rat anti-AChR antibody titers and by a reduced number of B-cells compared with control treatment.

The collaboration between T- and B-cells is thought to be critical in the generation of the class-switched, affinity-matured pathogenic autoantibodies in gMG. Dysregulated immune processes involving CD4+ T cells such as Th17 and T-follicular helper cells and various B-cell subsets have been implicated in the production of autoantibodies and secretion of proinflammatory cytokines.

Satralizumab has proven to be highly efficacious in NMOSD (Section 1.4), another chronic autoimmune disease, which shares several common features with MG. NMOSD and MG are mediated by pathogenic autoantibodies against the AQP4 and proteins at the postsynaptic portion of the NMJ (AChR, MuSK, and LRP4), respectively. In both diseases the immunopathogenic mechanisms include the breakdown of tolerance, the collaboration of T-cells and B-cells, imbalances in Th1, Th2, Th17, and Treg cells, aberrant cytokine and antibody secretion, and complement system activation (Wang and Yan 2017). Evidence of increased IL-6 levels has been reported in the cerebrospinal fluid of patients with NMOSD (Uzawa et al. 2009) and in the muscle tissue in patients with MG (Maurer et al. 2015). In addition, a recent comparison of peripheral blood B-cell subset ratios and B-cell–related cytokine levels showed that serum IL-6 levels were significantly higher in patients with gMG (anti-AChR–seropositive MGFA Grade II–IV) compared to healthy controls (Hu et al. 2020). Serum IL-6 levels were shown to be significantly increased in AChR+ MG and were correlated with MG disease severity, suggesting that IL-6 is involved in the pathogenesis of MG (Uzawa et al. 2021).

Tocilizumab, a blocker of IL-6 signaling, has been shown to have a beneficial effect in 2 female patients with moderate and severe AChR+ MG and insufficient response to rituximab (Jonsson et al. 2017). Both patients—who had failed at least two IST/immunomodulatory therapies, including prednisone and maintenance IVIg—displayed a beneficial response to tocilizumab with lowered Quantitative Myasthenia Gravis (QMG) scores and improved muscle strength. The treatment with this IL-6 inhibitor was well tolerated without reported adverse events.

These data identify IL-6 as an important target for modulation of autoimmune response in MG and suggest an IL-6 inhibitor may have a therapeutic benefit for patients with gMG.

1.5.2 Satralizumab Dose Selection

The 120 mg Q4W dosing regimen was shown to be safe and efficacious in the Phase III NMOSD studies. As expected for a monoclonal antibody, a clear correlation between body weight and exposure was observed, and although most patients achieved near maximal IL-6R occupancy throughout the dose interval, those patients with lower receptor occupancy (RO) values generally weighed > 100 kg.

The dosing regimen proposed for this study in gMG is therefore 120 mg Q4W for patients ≤ 100 kg, and 180 mg Q4W for patients > 100 kg. The intention of this dosing regimen is to achieve exposures associated with near maximal RO across the body weight range in gMG. PK parameters in adolescent patients with NMOSD were similar to those in adult patients, and the predicted exposures resulting from this dosing regimen are supported by the existing safety profile established in the Phase III studies in adult and adolescent patients with NMOSD.

Please refer to Section 3.4.1 for further details.

1.5.3 Study and Primary Analysis Population

The analysis considers two analysis populations: the AChR antibody seropositive (AChR+) population and the overall population (OP). The primary analysis will be performed in the AChR+ population. Each efficacy analysis *for the DB period* will be conducted on all randomized patients that have completed at least one postbaseline Myasthenia Gravis Activities of Daily Living (MG-ADL) assessment (modified intent-to-treat [mITT] population).

The pleiotropic role of IL-6 suggests that satralizumab may be efficacious in patients with gMG irrespective of antibody type. AChR and LRP4 antibodies are produced by long-lived plasma cells, whereas MuSK IgG4 antibodies are presumably secreted by short-lived circulating plasmablasts. IL-6 is a pro-inflammatory cytokine with pleiotropic functions including induction of the differentiation and proliferation of pro-inflammatory Th17 cells and plasmablasts, and plasma cell maturation. Therefore, IL-6 blockade has the potential to modulate the immunopathogenic mechanisms of gMG irrespective of autoantibody type.

1.5.4 Overview of Risks and Safety Measures

The potential risks associated with satralizumab treatment in patients with gMG are based on the clinical experience with satralizumab in ongoing and completed studies in NMOSD, as well the safety information from other anti-IL-6R antibodies. An overview of the anticipated safety risks for satralizumab is provided below. Additional details on the

individual risks are provided in Section 5.1.1 and the Satralizumab Investigator's Brochure.

- Infections: Treatment with IL-6R inhibitor may increase risk of infections, including serious infections. IL6-R inhibitors suppress acute phase reactions (fever, increase in C-reactive protein [CRP], etc.) induced by IL-6, which may delay the detection of infection
- Serious hypersensitivity reactions: Anaphylaxis and hypersensitivity reactions are considered a potential risk for all biologic medications, including satralizumab

The following lab abnormalities have been observed in patients treated with satralizumab:

- Liver enzyme and bilirubin elevations
- Neutropenia
- Thrombocytopenia
- Elevations in lipid levels

Other laboratory abnormalities including decrease in CRP, fibrinogen and complements have been observed in patients treated with satralizumab and are anticipated pharmacodynamic (PD) effects. In addition, blockade of IL-6 signaling by satralizumab may result in normalization of CYP450 activity and therefore increases the metabolism of CYP450 substrates. Caution should be exercised in patients receiving CYP450 substrates, as doses may need to be adjusted.

In addition to the risks above, the following risks are potential risks for drugs in the same class:

- Gastrointestinal (GI) perforation (complication of diverticulitis)
- Malignancies
- Demyelinating disorders

Several measures will be taken to manage these risks and to ensure the safety of patients participating in this study:

- Patients who may have an increased safety risk will be excluded from the study (see Section 4.1.2.3)
- Regular standard safety evaluations (laboratory measures, physical examinations, vital sign measurements and ECG) will be performed throughout the study, with a special focus on monitoring the risks that have been previously associated with satralizumab or other IL-6R inhibitors (see Section 5.1.1).
- An independent Data Monitoring Committee (iDMC) will perform periodic safety data review during the DB period in an unblinded manner and, based on the review, will make recommendations on study conduct.

1.5.5 Benefit–Risk Assessment

Overall, the benefit–risk profile of investigation of satralizumab in a population of patients with gMG is considered favorable based on the following:

- Preclinical evidence of a key role of IL-6 in the autoimmune response to AChR and in pathogenesis of EAMG
- Similarities between NMOSD and gMG
- Case reports indicating beneficial effects of IL-6R blockade in patients with gMG
- Satralizumab as monotherapy or as a combination with OCS (15 mg of prednisolone equivalent per day), azathioprine, or mycophenolate mofetil was efficacious and well tolerated in patients with NMOSD in the Phase III clinical Studies BN40898 and BN40900

All necessary measures will be taken to closely monitor the safety of the patients enrolled in this study.

An assessment was conducted to determine whether there is any impact of the coronavirus disease 2019 (COVID-19) pandemic on the benefit-risk assessment of this study protocol, including, but not limited to, the patient population under study, study treatment and/or treatment combination being evaluated. Based on that assessment, the safety monitoring, management guidelines, and the risk mitigation measures provided in the study protocol are considered adequate.

With reference to COVID-19 vaccines, an assessment was conducted to determine whether there is any impact of the COVID-19 vaccines on the benefit–risk assessment of this study protocol. General information for vaccines provided in Sections 4.4.5 and 5.1.1.1 are also applicable to COVID-19 vaccines.

Based on this assessment, no additional risk mitigation measures related to COVID-19 vaccination are proposed at this time. The recommendations and management plan provided in the study protocol are considered adequate.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of satralizumab compared with placebo in patients with gMG on stable background therapy. In addition, the study will assess the long-term safety and efficacy of satralizumab during the open-label extension (OLE) period.

In this protocol, "study treatment" refers to satralizumab or placebo (assigned in addition to background therapy).

Specific objectives and corresponding endpoints of the DB period and the OLE are outlined in Table 2 and Table 3, respectively. The hierarchy of secondary endpoints *is listed in Section 6.4.3*.

Table 2 Objectives and Endpoints during the Double-Blind Period

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of satralizumab versus placebo on function in daily life in the AChR+ population	• Mean change from baseline in total MG-ADL score at Week 24
Secondary Efficacy Objectives	**Corresponding Endpoints**
• To evaluate the efficacy of satralizumab versus placebo on function in daily life in the OP	• Mean change from baseline in total MG-ADL score at Week 24
• To evaluate the efficacy of satralizumab versus placebo in the AChR+ population and OP on:	
– Function in daily life	• Percentage of patients with a ≥2-point reduction from baseline in total MG-ADL score at Week 24[a]
– QMG, QoL, and Fatigue	• Mean change from baseline in QMG score, MG-QOL 15r total score and Neuro–QoL Fatigue Subscale total score at Week 24 • Percentage of patients with a ≥3-point reduction from baseline in QMG score at Week 24[a]
– Clinical status	• Mean change from baseline in total MGC score at Week 24 • Percentage of patients with a ≥3-point reduction from baseline in total MGC score at Week 24 [a]
– Disease severity	• Proportion of patients: – Who have achieved minimal disease manifestation (total MG-ADL score of 0 or 1) at Week 24 [a] – With at least one gMG-related exacerbation between baseline and Week 24 – Receiving rescue therapy between baseline and Week 24 • Annualized rate of gMG-related exacerbations
• To evaluate the durability of the efficacy of satralizumab versus placebo in the AChR+ population and the OP	• Duration (average number of consecutive months) of meaningful improvement, defined as ≥2-point reduction from baseline in total MG-ADL score [a]

AChR=acetylcholine receptor; AChR+ =AChR-antibody seropositive (patients/population); ADA=anti-drug antibody; AUC=area under the concentration–time curve; CL/F=apparent clearance; C_{trough}=trough concentration; gMG=generalized myasthenia gravis; IL-6=interleukin-6; MG=Myasthenia gravis; MG-ADL=Myasthenia Gravis Activities of Daily Living; MGC=Myasthenia Gravis Composite; MG-QOL 15r=Myasthenia Gravis Quality of Life 15 Scale (revised); NCI CTCAE v5.0=National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; Neuro–QoL=Quality of Life in Neurological Disorders; OP=overall population; PD=pharmacodynamic; PK=pharmacokinetic; QMG=Quantitative Myasthenia Gravis; QoL=quality of life; sIL-6R=soluble interleukin-6 receptor; V/F=apparent volume of distribution.

[a] Patients who receive rescue therapy will be considered non-responders

Table 2 Objectives and Endpoints during the Double-Blind Period (cont.)

Exploratory Efficacy Objectives	Corresponding Endpoints
• To evaluate the efficacy of satralizumab versus placebo in the AChR+ population and OP on:	
– Severity of gMG exacerbations	• Severity of gMG-related exacerbations • Proportion of patients with at least one gMG-related exacerbation leading to hospitalization between baseline and Week 24 • Annualized rate of gMG-related exacerbations leading to hospitalization
– Time-to-event	• Time to disease improvement as measured by: – ≥2-point reduction in total MG-ADL score or – ≥3-point reduction in QMG score or – ≥3-point reduction in total MGC score or – MG-ADL score of 0 or 1 • Time to disease worsening as measured by the time from baseline to: – Start of rescue therapy – gMG-related exacerbation – Hospitalizations related to gMG exacerbation
– QoL	• Mean change from baseline to Week 24 in EuroQoL EQ-5D-5L Health Utility Index score
Safety Objective	**Corresponding Endpoints**
• To evaluate the safety of satralizumab versus placebo	• Incidence and severity of adverse events, with severity determined according to NCI CTCAE v5.0 grading • Change from baseline in targeted vital signs, ECG results, physical examination findings, targeted clinical laboratory test results, and suicidality
Pharmacodynamic Objective	**Corresponding Endpoint**
• To confirm target engagement and pathway inhibition in response to satralizumab	• Absolute values and change from baseline in serum levels of biomarkers IL-6 and sIL-6R

AChR = acetylcholine receptor; AChR+ = AChR-antibody seropositive (patients/population); ADA = anti-drug antibody; AUC = area under the concentration–time curve; CL/F = apparent clearance; C_{trough} = trough concentration; gMG = generalized myasthenia gravis; IL-6 = interleukin-6; MG-ADL = Myasthenia Gravis Activities of Daily Living; MGC = Myasthenia Gravis Composite; MG-QOL 15r = Myasthenia Gravis Quality of Life 15 Scale (revised); NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; Neuro–QoL = Quality of Life in Neurological Disorders; OP = overall population; PD = pharmacodynamic; PK = pharmacokinetic; QMG = Quantitative Myasthenia Gravis; QoL = quality of life; sIL-6R = soluble interleukin-6 receptor; V/F = apparent volume of distribution.

[a] Patients who receive rescue therapy will be considered non-responders

Table 2 Objectives and Endpoints during the Double-Blind Period (cont.)

Pharmacokinetic Objective	Corresponding Endpoints
• To investigate the pharmacokinetics of satralizumab by evaluating plasma exposure over 24 weeks	• Serum concentrations of satralizumab (mean and SD of C_{trough}) at specified timepoints • Estimates of primary PK parameters (e.g., CL/F and V/F) and secondary PK parameters (e.g., AUC) derived using population–PK modeling
Exploratory Pharmacokinetic Objective	**Corresponding Endpoints**
• To evaluate potential relationships between drug exposure and the efficacy and safety of satralizumab	• Relationship between selected covariates and exposure to satralizumab • Relationship between serum concentration or PK parameters for satralizumab and efficacy endpoints, PD biomarkers and safety endpoints
Immunogenicity Objective	**Corresponding Endpoint**
• To evaluate the immune response to satralizumab	• Prevalence of ADAs at baseline and incidence of ADAs during the study
Exploratory Immunogenicity Objective	**Corresponding Endpoint**
• To evaluate potential effects of ADAs on efficacy, biomarker, safety, and PK endpoints	• Relationship between ADA status and efficacy, biomarker, safety or PK endpoints
Exploratory Biomarker Objective	**Corresponding Endpoint**
• To identify and/or evaluate biomarkers that are predictive of response to satralizumab, can provide evidence of satralizumab activity, or can increase the knowledge and understanding of disease biology	• Relationship between biomarkers in blood and efficacy endpoints.

AChR = acetylcholine receptor; AChR+ = AChR-antibody seropositive (patients/population); ADA = anti-drug antibody; AUC = area under the concentration–time curve; CL/F = apparent clearance; C_{trough} = trough concentration; gMG = generalized myasthenia gravis; IL-6 = interleukin-6; MG-ADL = Myasthenia Gravis Activities of Daily Living; MGC = Myasthenia Gravis Composite; MG-QOL 15r = Myasthenia Gravis Quality of Life 15 Scale (revised); NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; Neuro–QoL = Quality of Life in Neurological Disorders; OP = overall population; PD = pharmacodynamic; PK = pharmacokinetic; QMG = Quantitative Myasthenia Gravis; QoL = quality of life; sIL-6R = soluble interleukin-6 receptor; V/F = apparent volume of distribution.

[a] Patients who receive rescue therapy will be considered non-responders

Table 3 Objectives and Endpoints during the Open-Label Extension Period

Safety Objective	Corresponding Endpoints
• To evaluate the long-term safety and tolerability of satralizumab	• Incidence and severity of adverse events, with severity determined according to NCI CTCAE v5.0 grading • Change from baseline in targeted vital signs, ECG results, physical examination findings, targeted clinical laboratory test results, and suicidality
Efficacy Objectives	**Corresponding Endpoints**
• To assess the efficacy of satralizumab in the AChR+ population and OP	• Mean change from active treatment baseline in: – MG-ADL total score – QMG score – MGC score – MG-QOL 15r score • Percentage of responders [a] based on: – ≥2-point reduction in total MG-ADL score or – ≥3-point reduction in QMG score or – ≥3-point reduction in total MGC score • Proportion of time and duration that patients show a meaningful improvement, defined as a ≥2-point reduction from active treatment baseline in total MG-ADL score • Number and severity of gMG-related exacerbations
• To assess the effect of satralizumab on steroid/IST/AChEI dose modification in the AChR+ population and OP	• The proportion of patients who maintain clinical response without increase in symptomatic medication dose and are able to reduce corticosteroid dose or withdraw from corticosteroid or IST during the OLE
Exploratory Efficacy Objective	**Corresponding Endpoint**
• To evaluate the efficacy of satralizumab versus placebo on additional QoL	• Mean change from baseline in Neuro–QoL Fatigue Subscale total score and EuroQoL EQ–5D–5L Health Utility Index score

AChEI = acetylcholinesterase inhibitor; AChR = acetylcholine receptor; AChR+ = AChR-antibody seropositive (patients/population); ADA = anti-drug antibody; AUC = area under the concentration–time curve; CL/F = apparent clearance; C_{trough} = trough concentration; IL-6 = interleukin-6; IST = immunosuppressant; MG-ADL = Myasthenia Gravis Activities of Daily Living; MG-QOL 15r = Myasthenia Gravis Quality of Life 15 Scale (revised); NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; Neuro–QoL = Quality of Life in Neurological Disorders; OLE = open-label extension; OP = overall population; PD = pharmacodynamic; PK = pharmacokinetic; QMG = Quantitative Myasthenia Gravis; QoL = quality of life; sIL-6R = soluble interleukin-6 receptor; V/F = apparent volume of distribution.

Table 3 Objectives and Endpoints during the Open-Label Extension Period (cont.)

Pharmacokinetic Objective	Corresponding Endpoints
• To investigate the pharmacokinetics of satralizumab by evaluating plasma exposure in the OLE	• Serum concentrations of satralizumab (mean and SD of C_{trough}) • Estimates of primary PK parameters (e.g., CL/F and V/F) and secondary PK parameters (e.g., AUC) derived using population–PK modeling
Immunogenicity Objective	Corresponding Endpoint
• To evaluate the immune response to satralizumab	• Prevalence of ADAs at baseline and incidence of ADAs during the OLE
Pharmacodynamic Objective	Corresponding Endpoint
• To confirm target engagement and pathway inhibition in response to satralizumab	• Absolute values and change from baseline in serum levels of PD biomarkers IL-6 and sIL-6R
Exploratory Biomarker Objective	Corresponding Endpoint
• To identify and/or evaluate biomarkers that can provide evidence of satralizumab activity, can aid in characterizing the mechanism of action, or can increase the knowledge and understanding of disease biology	• Relationship between biomarkers in blood and efficacy endpoints

AChEI = acetylcholinesterase inhibitor; AChR = acetylcholine receptor; AChR+ = AChR-antibody seropositive (patients/population); ADA = anti-drug antibody; AUC = area under the concentration–time curve; CL/F = apparent clearance; C_{trough} = trough concentration; IL-6 = interleukin-6; IST = immunosuppressant; MG-ADL = Myasthenia Gravis Activities of Daily Living; MG-QOL 15r = Myasthenia Gravis Quality of Life 15 Scale (revised); NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; Neuro–QoL = Quality of Life in Neurological Disorders; OLE = open-label extension; OP = overall population; PD = pharmacodynamic; PK = pharmacokinetic; QMG = Quantitative Myasthenia Gravis; QoL = quality of life; sIL-6R = soluble interleukin-6 receptor; V/F = apparent volume of distribution.

3. STUDY DESIGN

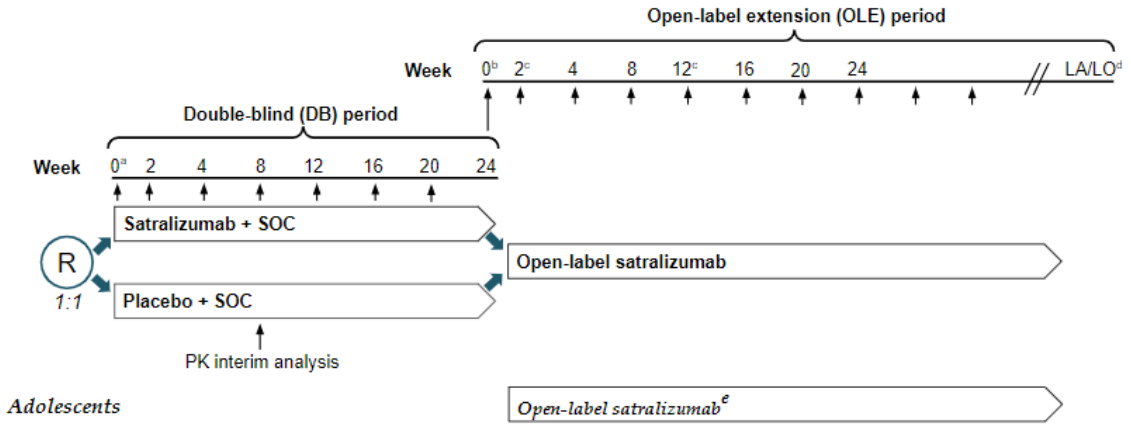
3.1 DESCRIPTION OF THE STUDY

This Phase III, randomized, DB, placebo -controlled, multicenter study is designed to evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of satralizumab compared with placebo as add-on therapy to standard of care (SOC) for the treatment of gMG. The study will include a 28-day screening period, a 24-week DB treatment period, and approximately 2-year OLE period after the last patient initiates open-label treatment. *As of global protocol Version 5, adolescents will be enrolled directly into the OLE period after completion of the screening period (see Section 3.1.3 for details).*

During the screening period, patients' eligibility for study participation will be evaluated. The 28-day screening period may be extended, in exceptional circumstances, but cannot exceed 42 days. A complete blood count (e.g., white blood cells, neutrophils, and *PK*

platelets) and liver test (ALT, AST and bilirubin) must be within 28 days prior to baseline. Figure 1 presents an overview of the study design. The schedule of activities is provided in Appendix 1 and Appendix 2.

Figure 1 Study Design



DB = double-blind; LA = last assessment; LO = last observation; OLE = open-label extension; PK = pharmacokinetic; *R = randomization*; SOC = standard of care

[a] Week 0 baseline assessments will be collected pre-dose.

[b] Week 0 of OLE period coincides with Week 24 of DB period.

[c] Patients treated with active drug in DB period will be administered a placebo dose at Week 2 of the OLE period to maintain blinding of treatment assignment in the DB period.

[d] The length of OLE period is approximately 2 years after the last patient enters OLE or approximately 4 years after the first patient enters the OLE. *Further details are provided in Section 3.2.*

[e] *Adolescent patients will be enrolled directly into the OLE period (after completion of screening; see Section 3.1.3) and will receive open-label satralizumab SC loading doses at Weeks 0, 2, and 4 in the OLE, followed by maintenance doses Q4W thereafter during the OLE period.*

3.1.1 Double-Blind Period

During the DB treatment period, patients will be randomized in a 1:1 ratio to receive either 120 mg or 180 mg satralizumab, as determined on the basis of body weight (Group A), or placebo (Group B) for 24 weeks (*see Figure 1*). Randomization will be stratified based on the following:

- Baseline SOC treatment: AChEI monotherapy and/or an OCS versus a steroid-sparing IST monotherapy or a combination of a steroid-sparing IST with other treatments (an AChEI and/or an OCS)
- Autoantibody type: AChR antibody-positive versus AChR antibody-negative (includes MuSK antibody- or LRP4 antibody-positive)
- Region: North America versus Europe versus rest of world.

Blinded study drug will be administered subcutaneously to patients at Weeks 0, 2, 4, and Q4W thereafter until the end of the DB period in addition to background treatments at a stable dose (see Section 4.1.1).

An interim analysis of pharmacokinetic (PK) data *was* performed when approximately 30 patients completed a minimum of 8 weeks of DB treatment (*including* approximately 15 patients from the satralizumab group). The purpose of the interim analysis *was* to confirm that the achieved exposure to satralizumab (and predicted RO) *was* within the target range. The background therapies permitted in this study are AChEI alone or the following therapies (with or without AChEI): OCSs, one IST, and an OCS in combination with one IST. Patients should remain on stable dose of background therapy throughout the DB period and until Week 12 of the OLE, with the exception of the last AChEI dose taken prior to in-clinic visits. AChEIs should not be taken for 10 hours prior to completion of efficacy assessments at each study visit (except screening visit), including QMG and MGC testing, if medically safe to do so. The permitted IST drugs are azathioprine, mycophenolate mofetil, tacrolimus, and cyclosporin A (see Section 4.4.1).

Following the interim analysis of PK data, the iDMC recommended that the initially proposed doses (120 mg ≤100 kg >180 mg) should be retained and that the Sponsor should continue the study without dose modification. Further details on the interim analysis of PK data are provided in Section 6.11.2.

3.1.2 Independent Data Monitoring Committee

An iDMC will be used during the DB period and until the database lock for the primary analysis. The iDMC will perform periodic (approximately every 3 months) unblinded safety reviews and make recommendations on trial continuation or modification. The iDMC *was* involved in the interim PK analysis as detailed in Section 6.11.2. All summaries and analyses will be prepared by the independent Data Coordinating Center (iDCC) and presented by treatment group for the iDMC's review. Members of the iDMC and iDCC will be external to the Sponsor and the study team and will follow a charter that outlines their roles and responsibilities. The Sponsor will remain blinded. Interactions between the iDMC and Sponsor will be carried out as specified in the iDMC Charter.

3.1.3 *Adolescent Patients*

As of global protocol Version 5, all adolescent patients enrolled into the study will directly enter the OLE period after completion of screening (see Figure 1).

Adolescent patients enrolled directly into the OLE will remain on stable background therapy until Week 24 of the OLE (Section 3.4.8).

Adolescent patients enrolled through previous versions of the protocol (prior to global protocol Version 5) will continue in the study as follows:

- *Adolescent patients randomized in the DB period prior to the randomization of the last adult patient in the DB period will continue on randomized, DB study drug for 24 weeks and can then enter the OLE period (after completion of the DB period) to start open-label satralizumab, remaining on stable background therapy until Week 12 OLE*

- *Adolescent patients randomized in the DB period after the randomization of the last adult patient in the DB period will enter the OLE period (without completion of DB period) to start open-label satralizumab, remaining on stable background therapy until Week 12 OLE*

3.1.4 Open-Label Extension Period

Patients who complete the DB period can enter the OLE period. *As of global protocol Version 5, adolescent patients will directly enter the OLE period after completion of screening (see Section 3.1.3).* Patients who experience a clinical exacerbation that requires rescue therapy during the DB period may continue in the study until the end of the DB period and can enter the OLE period upon completion of treatment and assessments in the DB period.

For adult and adolescent patients who complete the DB period, the final visit of the DB period coincides with the Week 0 visit of the OLE period and is, therefore, considered the OLE baseline. The assessments performed at Week 24 of the DB period will be used as the active treatment baseline for the patients who receive placebo during the DB period and as the OLE baseline for patients who receive satralizumab during the DB period. Upon completion of the Week 24 assessments all patients will receive open-label treatment with satralizumab.

In the OLE period, all patients will receive open-label treatment with 120 mg or 180 mg satralizumab, as determined based on body weight. Patients who receive placebo during the DB period will receive satralizumab SC loading doses at Week*s* 0, 2, and 4 in the OLE, followed by maintenance doses Q4W thereafter during the OLE period. Patients who receive active treatment during the DB period will continue receiving SC satralizumab Q4W during the OLE period but will receive an additional placebo SC injection at Week 2 to maintain blinding to DB treatment assignment.

For adult and adolescent patients who first enter the study randomized in the DB period, to ensure a period of satralizumab treatment stability in patients previously treated with placebo, dose reduction (taper) of background therapy (OCS, IST, and/or AChEIs) can be started at or after Week 12 of the OLE period *at the discretion of the investigator*.

Adolescent patients who first enter the study in the OLE period will receive satralizumab SC loading doses at Weeks 0, 2, and 4 in the OLE, followed by maintenance doses Q4W thereafter.

Further details on adolescent patients in the OLE period are provided in Sections 3.1.3 and 3.4.8.

3.1.5 Unscheduled Visits and Rescue Therapy

Unscheduled visits can be performed at the discretion of the treating neurologist.

If a suspected gMG exacerbation occurs during the study, the participant should return to the study site and undergo the following evaluations before or immediately after any administration of the rescue therapy: MG-ADL, QMG, Myasthenia Gravis Composite

(MGC), and Myasthenia Gravis Quality of Life 15 Scale (revised) (MG-QOL 15r). Additional assessments, such as hematology, chemistry, and urinalysis, will be performed if an infection or a metabolic disturbance is suspected to be contributing to the clinical presentation necessitating the unscheduled visit.

MG exacerbation requiring rescue therapy is defined as one of the following:

- MG crisis (Sanders et al. 2016)
- Substantial symptomatic worsening that requires immediate therapy
- Health in jeopardy if rescue therapy is not given, as determined by the treating physician.

Rescue therapy includes IVIg and PE with or without high -dose corticosteroids as outlined in Section 4.3.3. The choice of rescue therapy will be determined by the investigator on the basis of his or her overall clinical assessment.

Study drug administration will be continued as scheduled, concurrently with rescue therapy, unless the investigator considers it necessary to interrupt or discontinue study treatment (see Section 5.1.4). Patients who receive PE as rescue therapy will receive loading doses of study drug as soon as possible post -PE. Site staff should consult the Medical Monitor as to how to schedule dosing in such circumstances.

Patients who receive rescue therapy during the DB period may receive OLE satralizumab after completion of the DB period.

3.1.6 Safety Follow-Up

Patients who discontinue study treatment during the DB period for any reason should continue with the remaining assessments defined in the protocol. All efforts will be made to minimize missing data. However, patients who are unwilling to return to the clinic for all assessments will be asked to complete an end of treatment (EOT) visit within 4 weeks and a safety follow-up (SFU) visit 12 weeks after the final dose of study drug.

Patients who discontinue study treatment during the OLE period will be asked to complete *an* EOT visit *within* 4 weeks and *a* SFU visit 12 weeks after the final dose of study drug. Patients who decide to continue treatment with satralizumab outside of this study will have to complete the EOT visit, but they will not have to complete the SFU or end of study visit.

For patients aged ≥ 12 to < 18 years at the time of informed consent, who withdraw from the study or complete the extension period, an additional follow-up assessment will be conducted at 24 weeks after the final dose of study drug.

3.1.7 Number of Patients and Study Regions

The study will be conducted at approximately 120 sites in about 19 countries, including but not limited to, North America, Europe, Latin America, and Asia.

This study will initially enroll *approximately 160 AChR +patients, and up to 25 MuSK +/LRP4 +patients,* including *adults and* adolescents aged ≥ 12 years to *< 18* years old with gMG across all sites. *Only adult patients aged ≥18 years old will be included at participating sites in France.*

After completion of the global enrollment phase, additional *adolescent* patients may be enrolled in *the OLE period*.

3.1.8 *Patient Input into Study Design*

Adolescent patients diagnosed with MG and their caregivers from different organizations within the patient community were interviewed and asked to provide feedback on the following aspects of the study:

- *Study design, endpoints, inclusion and exclusion criteria activities, and patient-reported outcomes (PROs)*
- *Recruitment and retention (e.g., inclusivity of underserved patient communities, potential recruitment challenges, possible retention challenges).*

This feedback was taken into consideration when developing the protocol.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient, last visit (LPLV), occurs (i.e., last patient in the global study phase) or the date at which the last data point required for statistical analysis or SFU is received from the last patient (global enrollment phase), whichever occurs later. The LPLV is expected to occur approximately 2 years after the last patient in the global study phase enters the OLE period.

For adolescent patients enrolled directly in the OLE, the LPLV is expected to occur approximately 2.5 years after the last adolescent patient is enrolled in the adolescent OLE.

The end of the DB study period is expected to occur 24 weeks after the last patient in the global study phase is enrolled. The duration of the OLE period is estimated to be approximately 2 years from the last global study phase patient entering the OLE and approximately *4* years from the first patient entering this phase. *The total length of study, from screening of the first patient to the end of the adolescent OLE period, is estimated to be approximately 6 years.*

3.3 *DURATION OF PARTICIPATION*

The total duration of study participation for each individual enrolled in the DB period is expected to be approximately 2.5–4 years, depending on when the participant enters the OLE and the duration of time the participant spends in this period.

The total duration of study participation for adolescent patients enrolled directly in the OLE is expected to be approximately 2–3.5 years, according to the estimated recruitment timelines.

3.4 RATIONALE FOR STUDY DESIGN

3.4.1 Rationale for Satralizumab Dose and Schedule

Weight-tiered dosing via SC injection will be used in this study for the investigation of efficacy and safety of satralizumab in gMG as shown in Table 4.

Table 4 Dosing Regimen for Investigation in Phase III Study of Satralizumab for the Treatment of Generalized Myasthenia Gravis

Body Weight at Baseline [a]	Dose and Regimen
≤ 100 kg	120 mg administered at Weeks 0, 2, 4, and Q4W thereafter as a SC injection
> 100 kg	180 mg administered at Weeks 0, 2, 4, and Q4W thereafter as a SC injection

Q4W = every 4 weeks.

[a] Recommendations in case of changes in body weight in an individual patient would result in a different dosing band are given in Table 6.

The dose regimen is based on a combination of sources of information, including:

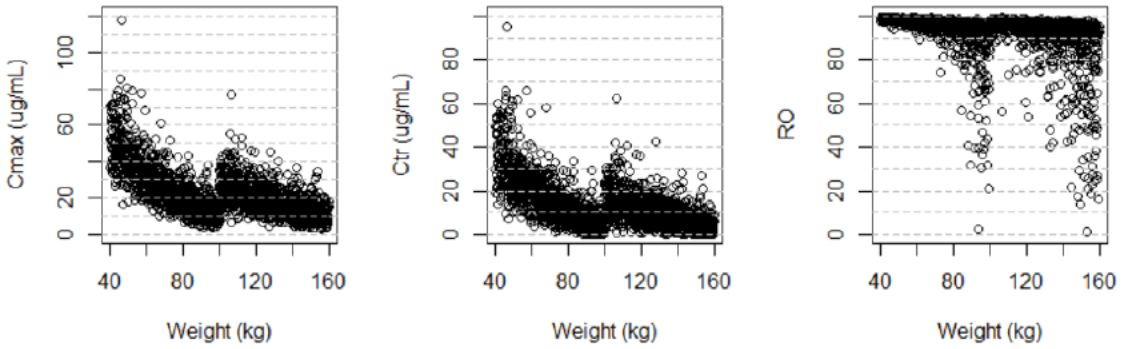
- PK, PD, and safety data for satralizumab for the initial development in NMOSD
- Consideration of differences in population demographics, particularly the greater incidence of males in the gMG population compared to NMOSD, resulting in greater representation of higher body weights.

The 120-mg fixed dose regimen investigated in the Phase III studies in NMOSD was associated with high predicted median trough receptor occupancy (≥ 95%) at steady-state ($RO_{tr,ss}$) values in most patients, and was shown to be safe and efficacious in all body weight groups. The few patients with predicted $RO_{tr,ss}$ values < 80% generally had baseline body weights > 100 kg.

Real-world data from a large U.S. emergency room-based dataset of 58,860 patients having an MG code suggest that approximately 30% of patients in this population may have body weights > 100 kg. Exposure similar to that in NMOSD is expected to be effective also in gMG, and therefore the Sponsor has performed simulations using the existing population-PK (pop PK) model, to estimate the dose required to achieve the same near-maximal $RO_{tr,ss}$ values achieved in patients with NMOSD throughout the dose interval for patients across the expected gMG body weight range.

The predicted maximum concentration observed (C_{max}), trough concentration (C_{trough}), and RO values in serum following administration of 120 mg Q4W and 180 mg Q4W in patients weighing ≤ 100 kg and > 100 kg, respectively, are shown in Figure 2. These simulations indicate that these regimens would be expected to achieve similar median C_{max} at steady state ($C_{max,ss}$) values and trough concentration at steady state ($C_{tr,ss}$) values to those observed in the NMOSD Phase III studies, which were associated with near maximal RO throughout the dose interval. The range of predicted exposures in patients weighing > 100 kg receiving 180 mg does not exceed the maximum exposures achieved in the Phase III trials in NMOSD, and therefore remains within the existing exposure–safety coverage. The proposed study design includes an interim PK analysis to confirm that the achieved exposures are within the target range.

Figure 2 Dependencies of Steady-State Exposure Parameters and Receptor Occupancy on Body Weight Following 120mg Q4W Dosing (Body Weight Range: 40–100 kg), and 180-mg Q4W Dosing (Body Weight Range: 100–160 kg)



ADA = anti-drug antibody; Cmax = maximum concentration observed at steady-state; C_{tr} = steady-state trough concentration; NMOSD = neuromyelitis optica spectrum disorder; Q4W = every 4 weeks; RO = receptor occupancy.

Notes: Plots show the results of simulation for 2000 individuals.

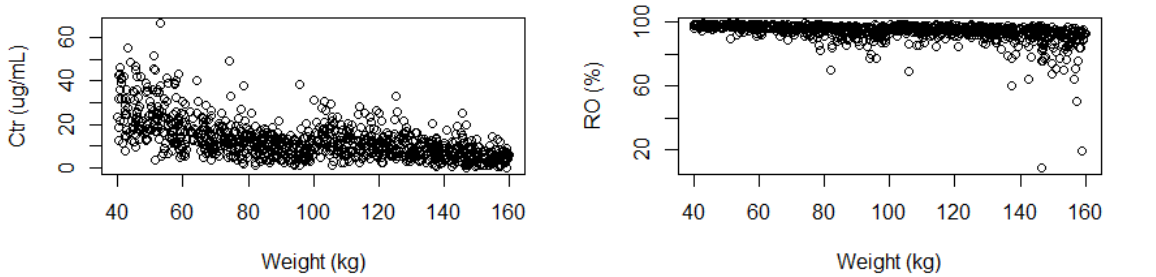
Predictions for C_{max} are shown on the left, C_{trough} in the middle, and RO on the right. Points are simulated data assuming ADA positivity in a similar proportion of patients as was observed in NMOSD studies. Dashed horizontal lines have been added for reference.

A favorable safety profile was demonstrated in the NMOSD program for satralizumab, supporting the targeting of similar exposures in this study. However, exposures below the target range may warrant an increase in dose to optimize IL-6 blockade throughout the dose interval across the expected body weight range. Therefore, an option for dose increase is included (for all body weight ranges, if warranted) in the study design. Further detail is provided in Section 3.4.11.

While most PK parameter estimates for satralizumab were shown to be very similar between healthy volunteers (HV) and patients with NMOSD, population differences in the total clearance of drug (CL) were observed (covariate value [95%CI] in HV 95.8%

[67.5 to 124.1]). PK simulation has therefore been used to explore potentially useful regimens in the case that CL in the gMG population is more representative of that observed in HV. The simulations presented in Figure 3 indicate that if that is the case, a dosing regimen of 180 mg and 240 mg for patients ≤ 100 kg and > 100 kg, respectively, would be expected to maintain the target level of RO across the body weight ranges. Provision is therefore made to adapt the dose to this higher dosing regimen if CL values in gMG are found to be reflective of those in HV.

Figure 3 Dependencies of Steady-State C_{trough} and Receptor Occupancy on Body Weight following 180-mg Q4W Dosing (Body Weight Range: 40–100 kg), and 240-mg Q4W Dosing (Body Weight Range: 100–160 kg)



C_{trough} = steady-state trough concentration; RO = receptor occupancy.

PK simulations will be used as part of the interim PK analysis to either confirm that the initially proposed doses achieve target exposures, or that the dose should be adapted to 180/240 mg regimen. In either case, the chosen dosing regimen will be associated with exposures that do not significantly exceed the existing exposure–safety coverage.

3.4.2 Rationale for Patient Population

3.4.2.1 Rationale for Choice of Disease Severity and Residual Disease Symptoms

This study will investigate the efficacy and safety of satralizumab in patients with generalized MG Class II, III, or IV[1] disease according to the MGFA classification system (see Appendix 14). Patients with MGFA Class V MG will be excluded from the study due to the severity and instability of the disease.

This Phase III study will enroll patients who are receiving a stable SOC treatment with suboptimal disease control, irrespective of their prior exposure and response to treatment with ISTs, including those who are newly diagnosed or treatment refractory (see Section 4.5.3 for definition). The aim of the study is to recruit a representative and generalizable population across the disease severities and treatment histories.

[1] *Patients with MG Class IV at participating sites in France are excluded from the study.*

The residual disease symptoms are defined by having a total score of ≥ 5 on the MG-ADL at screening with more than 50% of this score attributed to non-ocular items. This criterion was selected to allow for enrollment of gMG patients with sub-optimal disease control who may benefit from additional therapy.

3.4.2.2 Autoantibody Types and Diagnosis

The patients must be positive for anti-AChR, anti-MuSK or anti-LRP4 autoantibodies. The majority of patients with gMG have detectable antibodies against AChR (~85%), MuSK (~7%) or LRP4 (~ 3%) (Gilhus et al. 2019). Therefore, inclusion of all three serotypes allows for inclusion of the majority of patients with gMG. The study is expected to enroll approximately 80% AChR+ patients.

3.4.2.3 Rationale for Inclusion of Adolescent Patients

Clinical phenotypes in JMG and especially in post-pubertal patients are similar to adults. The main types of treatment for gMG are symptomatic treatment using AChEIs, immunosuppressive and immunomodulatory therapies, and thymectomy, which are also being used for treatment of juvenile gMG.

This Phase III study requires patients to be reliable witnesses in terms of assessment of disability and general health. Adolescents are considered capable of cooperating with trial procedures without invalidating study results.

Satralizumab has been studied in 9 adolescent patients with NMOSD aged 12 to < 18 years (6 out of 9 patients aged < 17 years) of age at the time of informed consent (mean age 15 years), of whom 7 were randomized in BN40898 prior to the clinical cut-off date of the Clinical Study Report (CSR). The safety profile of satralizumab in these pediatric patients with NMOSD (12 to < 18 years of age) was generally consistent with the profile observed in the adult population. All adverse events reported in adolescent patients were of mild or moderate severity and resolved. None of the adolescent patients discontinued the study due to an adverse event. Data obtained in patients with NMOSD patients aged 12 to < 18 years who received the adult dosing regimen (120 mg Q4W) show that popPK parameters for satralizumab are not significantly different from those in the adult population.

There is precedent for the use of an anti–IL-6R monoclonal antibody to treat pediatric patients, with and without concomitant immunosuppressant therapies. Tocilizumab is licensed for the treatment of systemic juvenile idiopathic arthritis and polyarticular juvenile idiopathic arthritis internationally and also for the treatment of Castleman's disease in Japan. The safety profile in clinical trials (approximately 519 pediatric patients < 18 years) and post-marketing setting (over 7500 pediatric patients) has been consistent with that in adults, and there have been no specific safety concerns identified in pediatric patients treated with tocilizumab.

Only adult patients aged ≥ 18 years old will be included at participating sites in France.

3.4.3 Rationale for Choice of Background Treatment

Patients on a stable dose of background therapy will be enrolled. The background SOC therapies permitted in the proposed study are:

- AChEI
- OCS
- One IST
- OCS in combination with one IST

Use of AChEI is permitted as monotherapy or concomitant treatment for patients on a stable dose with OCS, one IST, and OCS in combination with one IST. For detailed requirements on background therapy stable dose please refer to Section 4.4.1.

The combination treatment regimen of ISTs and/or OCS was chosen on the basis of being the most common treatment choice for gMG worldwide and in accordance with the international consensus guidance for management of MG (Sanders et al. 2016).

3.4.4 Rationale for Control Group

In this study placebo will be used as comparator to provide objective evidence of safety and efficacy data from patients exposed to the experimental therapy. Use of placebo will be in addition to SOC background therapy to avoid withholding of established treatment.

3.4.5 Rationale for Primary Outcome Measure: Myasthenia Gravis Activities of Daily Living

The primary objective for this study is to compare the efficacy of satralizumab added to SOC versus placebo added to SOC using the MG-ADL as a primary outcome measure.

The MG-ADL was developed by Wolfe and colleagues (1999) to assess the degree of gMG symptoms (six items: diplopia, ptosis, difficulties with chewing, swallowing, talking, and respiratory problems) and functional limitations in carrying out activities of daily living (two items: ability to brush teeth or comb hair and impairment in the ability to arise from a chair) that have been shown to be present and clinically relevant in gMG patients. Each of the eight items is ranked on a 0–3 scale yielding a total score that ranges from 0 to 24, with higher scores indicating greater disease severity (see Appendix 6). The items of the MG-ADL were all derived from the original 13-item symptom list that comprises the clinician-rated QMG scale.

The psychometric properties of the MG-ADL have been characterized. Construct validity has been demonstrated by showing correlations with the QMG (r=0.58; Wolfe et al. 1999), MGC measure (r=0.85), and the MG-QOL 15r measure (r=0.76) (Muppidi et al. 2011). Test–retest reliability was determined in a small sample (n = 26) of patients queried on two repeated assessments separated by 2–4 days and showed a high degree of reproducibility (r = 0.94) (Muppidi et al. 2011).

The importance of patient feedback given the fluctuating nature of the disease combined with the established psychometric properties, including good content validity associated with patients' functioning in daily life, renders MG-ADL an appropriate primary outcome measure.

This scale has been commonly used as primary objective in the recently completed studies of *eculizumab* (Howard et al. 2017)*, efgartigimod (Howard et al. 2021), rozanolixizumab (Bril et al. 2023), zilucoplan (Howard et al. 2023), ravulizumab (Vu et al. 2022), and amifampridine phosphate* (NCT03304054) *for gMG.*

3.4.6 Rationale for Secondary Outcome Measures

The QMG, MG-QOL15r, NeuroQOL-Fatigue scale, and the MGC have been selected as secondary endpoints in order to compare the efficacy of satralizumab added to SOC versus placebo added to SOC.

The QMG is a 13-item assessment of gMG symptom severity based on clinical examination (Tindall et al. 1987). It has been used in clinical trials since 1983, when it was first developed to study the relationship between AChR-Ab binding and disease severity (Besinger et al. 1983). More recently, the QMG has been used as a key secondary efficacy outcome measure in the recently completed studies of eculizumab (Howard et al. 2017*), efgartigimod (Howard et al. 2021), rozanolixizumab (Bril et al. 2023), zilucoplan (Howard et al. 2023), ravulizumab (Vu et al. 2022), and amifampridine phosphate* (NCT03304054) *for gMG.*

The QMG items assess severity of symptoms ranging from 0–3 for ptosis, diplopia, orbicularis oculi weakness, swallowing, speech disruption, percent forced vital capacity, arm and leg endurance (four items), grip strength (two items), and neck flexion strength, resulting in a total score that ranges from 0 to 39 with higher values indicating worse symptoms (Tindall et al. 1987).

The psychometric properties of the QMG have been studied using both observational and clinical trial data. The QMG has acceptable internal consistency (Cronbach's $\alpha = 0.74$) and test–retest reliability (intra-class correlation coefficient [ICC] = 0.88) in clinically stable patients (Barnett et al. 2015). Construct validity studies of the QMG have found correlations with the MGFA score ($r^2 = 0.54$) and the MG-QOL 15r ($r = 0.41$) (Barnett et al. 2012).

This study will evaluate the efficacy of satralizumab added to SOC versus placebo added to SOC by comparing the change from baseline in the QMG score at Week 24 (the end of the DB period).

The MGC is an additional secondary efficacy outcome measure in this trial. As the name implies, the MGC is a composite measure consisting of items drawn from the MG-ADL (chewing, swallowing, speech, and breathing), QMG (diplopia and ptosis), and

Manual Muscle Test (hip, neck, facial, and deltoid strength) in an effort to include both clinician- and patient-reported elements in a single measure (Burns et al. 2008). Each of the ten items contribute to a total score ranging from 0 to 50, with higher values indicating increasing symptom severity.

The psychometric properties of the MGC were evaluated in a primary care setting in 175 patients spread across 11 sites (Burns et al. 2010). Test–retest reliability was found to be high (0.98 correlation coefficient) in a small sample of patients from a single site ($n = 38$). The MGC exhibited moderate to strong convergent validity with the MG-ADL total score ($r = 0.85$), MG-QOL 15 total score ($r = 0.68$), and the Manual Muscle Test ($r = 0.8$).

Given that the MGC has fair psychometric properties and draws on both physician- and patient-reported items, the Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America has recommended its use in randomized clinical trials of potential new gMG therapies (Benatar et al. 2012).

As one of the secondary efficacy objectives, this study will evaluate the efficacy of satralizumab added to SOC versus placebo added to SOC by comparing the change from baseline in the MGC score at Week 24 (the end of the DB study period).

The MG-QOL-15 is a disease-specific health-related quality of life measure that consists of 15 items: mobility (9 items), symptoms (3 items), and contentment and emotional well-being (3 items). Items are scored on a Likert scale from 0 to 4 with the total score ranging from 0 to 60, where higher scores indicate worse HRQoL (Burns et al. 2008) The MG-QOL-15 has strong internal consistency reliability (Cronbach's $\alpha = 0.89$) and test–retest reliability (ICC = 0.98) (Burns et al. 2011). In a recent trial of mycophenolate mofetil in gMG, the MG-QOL-15 correlated well with the physical and mental summary components of the 36-Item Short Form Survey, as well as with MG-specific measures (QMG, MG-ADL) (Burns et al. 2008).

The MG-QOL-15 also demonstrated to be responsive in a randomized, controlled study of IVIg versus PE, where responders to treatment improved in average by nine points compared with non-responders, who changed by two points, thereby suggesting that a decrease MG-QOL-15 of seven or more points is correlated with improvement in the subgroup with moderate to severe MG (QMG score ≤ 11) (Barnett et al. 2013). The minimal important difference has not been fully determined. Based on its extensive use, the MG-QOL has been recently modified, to improve the performance of certain items (Burns et al. 2016). In the modified version (MG-QOL 15r) the 15 items were rescored from a 0–4 to a 0–2 scale, based on Rasch analysis. The resulting measure scores ranges from 0 to 30, and higher scores indicate worse health-related quality of life. When compared with the original scale, the modified version had better psychometric properties than the original and it is very easy to use (Burns et al. 2016).

The Neuro–QOL Fatigue scale is a short form that is part of a collection of instruments and item banks, developed through a National Institute of Neurological Disorders and Stroke–sponsored initiative to evaluate the HRQoL of adults and children diagnosed with neurological disorders (Cella et al. 2012). It consists of eight items, each using a 5-level Likert scale ranging between 1 = never to 5 = always, with a 7-day recall period. The measure has demonstrated strong internal consistency reliability (Chronbach's $\alpha = 0.97$) and construct validity (see Cella et al. 2012 for examples).

The scale has recently been validated in patients with MG using an observational cohort of 257 patients receiving either IVIg/PE or prednisone (Tran et al. 2018). The results demonstrated a positive relationship between fatigue and MG severity. Patients in MGFA Classes II–III exhibited mild to moderate fatigue, while those in Class IV experienced severe fatigue. Fatigue scores also correlated positively with MG Impairment Index, QMG, MGC, and MG-ADL (Pearson's r = 0.52–0.69), indicating acceptable convergent validity (Tran et al., 2018). All treatment groups showed a significant decrease in fatigue at Week 4 compared to baseline, with a standardized response mean for the overall population of 0.49, suggesting that the measure has good responsiveness (Tran et al. 2018).

The Neuro–QOL Fatigue scale was also used in the recent REGAIN study of eculizumab in patients with MG (Andersen et al. 2019).

3.4.7 Rationale for Secondary Responder Analysis

As part of the secondary efficacy objectives, the following supportive responder analyses for the MG-ADL, QMG, and MGC total scores will be performed.

The efficacy of satralizumab versus placebo at Week 24 based on percentage of patients with:

- A $\geq$ 2point reduction from baseline in total MG-ADL score with no rescue therapy received
- A $\geq$ 3point reduction from baseline in QMG score with no rescue therapy received
- A $\geq$ 3point reduction from baseline in total MGC score with no rescue therapy received

Additionally, the efficacy of satralizumab will be assessed by the durability and the onset of response using the above responder definitions.

3.4.7.1 MG-ADL Responder Definition

As noted in Section 3.4.5, the primary efficacy objective of this study will be evaluated by comparing the mean change from baseline in total MG-ADL score at Week 24.

In an evaluation of the responsiveness of the MG-ADL to changes in disease status, Muppidi and colleagues (2011) assessed gMG patients (n = 76) at two visits, 6 months apart, who underwent variable interventions. A gold standard was derived on the basis

of combined improvement in both the MG-QOL 15r and a 7-point physician global impression of change. Receiver operating curves (ROC) were derived based on the gold standard used to determine responsiveness, resulting in an area under the curve of 0.9 and suggesting a high degree of accuracy of the MG-ADL to predict clinical improvement. Sensitivity and specificity were calculated systematically for different thresholds of change in MG-ADL to determine the most accurate cut-off point for predicting clinical improvement based on the gold standard. A responder threshold of a 2-point reduction in the MG-ADL was found to be the most accurate predictor of improved clinical status (sensitivity = 77 and specificity = 82) (Muppidi et al. 2011).

3.4.7.2 QMG Responder Definition

The responsiveness of the QMG to changes in gMG clinical status has been shown in several clinical trials, yielding statistically significant differences between patients treated with active drug versus placebo (Tindall et al. 1987; Zinman et al. 2007). Katzberg and colleagues (2014) used data from a randomized clinical trial of gMG patients who received either placebo or IVIg therapy to derive estimates of the minimum clinically important difference (MCID) that can be used to classify responders (Katzberg et al. 2014). Using a combination of anchor- and distribution-based methods that showed strong convergence, they found an MCID threshold of ≥ 2 for QMG baseline severity between 0 and 16 and ≥ 3 for QMG baseline severity above 16.

3.4.7.3 MGC Responder Definition

The responsiveness of the MGC to changes in disease status was studied in 11 primary care centers with 151 patients receiving SOC as determined by their treating physician. Subsequent visits were separated by an average of 4.7 months (Burns et al. 2010). A gold standard was defined as improvement in both the physician's global impression of change and the MG-QOL 15r. ROC curve analysis using this gold standard, showed that a 3-point improvement in the MGC had optimal sensitivity and specificity (Burns et al. 2010).

3.4.7.4 Rescue Therapy Handling in the Responder Definition

As stated in Section 3.1.4 , the rescue therapies available will be IVIg, PE, and high-dose IV corticosteroids. Starting a rescue therapy constitutes a significant stand-alone event that would be triggered only by an exacerbation. Consequently, patients who receive rescue therapy will be considered non-responders.

3.4.8 Rationale for Open-Label Extension

Following the 24-week DB period, the study will include an OLE period of approximately 2 years from last patient in the global study. *Adolescent patients will be enrolled directly in the OLE after completion of screening (see Section 3.1.3).* The objectives of the OLE are to evaluate satralizumab long-term safety and efficacy, including steroid/IST sparing, in patients with gMG.

The adolescent OLE aims to evaluate pharmacokinetics, pharmacodynamics, safety, and efficacy of satralizumab in adolescents aged ≥12 years to <18 years old with gMG.

This study will enroll patients on stable background therapy, including OCSs and ISTs as indicated in Section 3.1.

Long-term steroid treatment is associated with numerous adverse effects on many organ systems, including bone (osteoporosis, avascular necrosis), muscle (myopathy), metabolism and endocrine organs (weight gain, impaired glucose tolerance, hypothalamic-pituitary-adrenal suppression), skin (skin atrophy, acne, striae), eyes (glaucoma, cataract), behavior and mood (mood disorders, insomnia), cardiovascular system (hypertension, fluid retention, perturbations of serum lipoproteins), GI system (gastritis, peptic ulcer disease), and immune system (increased risk of infection). One of the key treatment goals in MG is to reduce exposure to steroids (Sanders et al. 2016; Jaretzki et al. 2000). The adverse event profile of the steroid-sparing ISTs that constitute the background therapy in this study includes renal toxicity with the use of cyclosporine, myelosuppression, infections, liver toxicity, and malignancies (Vodopivec et al. 2014; Collins et al. 2019)

At or after Week 12 of the OLE, tapering of steroids and IST background treatment will be allowed based on clinical judgement *for adult and adolescent patients randomized in the DB period at study start.* Satralizumab dosing until Week 12 of the OLE is required to ensure that patients treated with placebo during the DB period have reached steady-state satralizumab concentrations.

Adolescent patients enrolled directly in the OLE will remain on stable background therapy until Week 24 of the OLE period.

The ability of patients to successfully taper steroids or ISTs while concurrently taking satralizumab will be evaluated in the OLE period based on analyses that will be pre-specified in the statistical analysis plan (SAP).

3.4.9 Rationale for Biomarker Assessments

This study will assess whether biomarkers, measured at baseline, can be used to identify patients with enhanced clinical benefit when treated with satralizumab or differential disease progression. The study will also assess whether biomarkers can aid in characterizing the mechanism of action of satralizumab in gMG, provide evidence of satralizumab activity in gMG, or increase the knowledge and understanding of gMG disease biology. Exploratory biomarker samples for research purposes to identify pathway and/or disease biomarkers may include, but may not be limited to, those reflective of inflammation, B- and T-cell subsets, activities, and products (e.g., serum IL-17 and B-cell subsets in blood).

PD biomarker samples will be collected for the assessment of target engagement (e.g., IL-6 and sIL-6R) in response to satralizumab treatment.

3.4.10 Rationale for PK Sample Collection Schedule

Samples to assess serum concentration of satralizumab will be taken prior to each administration during the DB period, and up to Week 24 of the OLE, followed by every 12 weeks for the remaining duration of treatment to explore the pharmacokinetics of satralizumab in the gMG population following longer term treatment. This assessment will include the impact of a range of covariates on exposure (e.g., gender, race, age, and body weight), and relationships between exposure and PD, efficacy, immunogenicity, and safety endpoints.

3.4.11 Rationale for Interim PK Analysis

Satralizumab PK- and PD-data collected from the Phase I study in patients with RA were used to inform dose-selection for Phase III studies in patients with NMOSD, and this regimen was shown to be safe and efficacious. While a similar approach to dose-selection is now proposed for this Phase III study in gMG, the Sponsor is mindful that population differences in the pharmacokinetics for satralizumab are possible. Therefore, the proposed Phase III design in gMG makes provision for an interim analysis of PK data, to ensure that patients are achieving target exposures while the Sponsor remains blinded, maintaining the integrity of this pivotal study.

An interim analysis of PK data *was* performed when approximately 30 patients completed a minimum of 8 weeks of DB treatment *(including* approximately 15 patients from the satralizumab group). The purpose of the interim analysis *was* to assess whether the achieved exposure to satralizumab (and predicted RO) is within the predicted range. The use of the existing PK model as the basis for prediction of RO in this interim analysis *was* considered appropriate given that the target is the same in both indications, and similar target expression is expected for gMG.

The proposed sample size for this PK interim analysis is supported by PK simulation. Simulation was performed assuming a CL parameter estimate similar to that observed in either NMOSD or in HV (the fastest CL observed in any population to date, and therefore associated with potentially the lowest absolute exposure). Two different scenarios for enrollment rate were also simulated and the sample size was varied between $n = 12-30$. The simulated data set contained the cumulative PK data available up to the time that the last patients completed 8 weeks of treatment. For each evaluated scenario, the percent of times with relative standard error on CL $>20\%$, percent of times with the CL estimate outside of 0.8–1.25 of the true value, and percent of times with the CL estimate outside of 0.6–1.44 of the true value were reported. The results are reported Table 5. The simulations indicate that PK data from approximately 15 patients could be expected to provide adequate precision ($<20\%$) and that the population clearance would be estimated to a value which is within 0.8–1.25 of true clearance more than 80% of the

cases (see results for n = 16). This takes into account that the PK interim analysis dataset will include all cumulative PK data available up to the time that the 15th patient receiving active drug completes 8 weeks of treatment. In the case that CL cannot be estimated with adequate precision (see above) on the basis of the cumulative dataset at this point, the PK interim analysis *could* be repeated based on the cumulative dataset after an additional 10 patients (to include approximately 5 receiving satralizumab) have completed 8 weeks of treatment.

Table 5 Precision and Bias for Generalized Myasthenia Gravis Clearance Estimate for Different Pharmacokinetic Interim Analysis Sample Sizes

Number of Patients	Percent of Estimation Runs with:		
	RSE > 20% [a]	CL Estimate Outside ratio of 0.8–1.25 of NMOSD Reference [b]	CL Estimate Outside Ratio of 0.6–1.44 of NMOSD Reference [b]
12	26.3	20.0	2
16	8.7	15.0	1.3
20	2.7	10.7	0.7
24	0	6.3	0.3
30	0	0.7	0

CL = total clearance of drug; NMOSD = neuromyelitis optica spectrum disorder; RSE= residual standard error.

[a] Estimate of precision, % of simulations with a RSE > 20% are displayed.

[b] Estimate of bias, % of simulations with an estimated value outside the specified ranges of the true value.

Throughout the study, and therefore for the PK interim analysis, patients of a range of bodyweights in proportions approximately representative of the overall gMG population is expected to be recruited.

A dose decision framework (including provision for a pre-specified alternative higher dose) *was* defined in a pharmacometric analysis plan prior to study start. This plan set out the criteria for predicted exposure and RO (derived using the existing pop PK model based on HV and NMOSD, updated following incorporation of the new data in gMG) with which decisions for selection of an adapted dose will be made. In case target exposures (based on those associated with near-maximal receptor occupancy in patients with NMOSD) *were* not achieved, the dose adaptation option *was* to increase the dose to the pre-defined dose regimen of 180 mg and 240 mg for patients ≤ 100 kg and > 100 kg, respectively. The rationale for this higher dose, in the case that CL values in gMG are reflective of those in HV (higher than those in the NMOSD population), is presented in Section 3.4.1.

Further details on the PK interim analysis are provided in Section 6.11.2.

3.4.12 Rationale for Immunogenicity Sample Collection

Anti-satralizumab antibodies (hereinafter referred to as ADAs) were detected in a large proportion of patients with NMOSD enrolled in the Phase III studies, with available data indicating that the probability of developing ADAs was positively correlated with low exposure and higher body weight. However, similar clinically-meaningful efficacy was demonstrated in all body weight groups in both Phase III studies.

Serum samples for ADAs will be taken in parallel to PK samples, with the objective of assessing the incidence and titer-time profile of ADAs in the gMG population, and the impact on exposure to satralizumab. ADA data will be included in the blinded review of PK data at Week 8, for the purpose of interpretation of the satralizumab concentration data, in addition to the subsequent analysis based on the full study dataset.

4. MATERIALS AND METHODS

4.1 PATIENTS

This study includes patients with gMG who are seropositive for anti-AChR, anti-MuSK or anti-LRP4 antibodies. The proportion of patients who are negative for anti-AChR antibodies at screening is estimated to be approximately *10-15*% of the total number of screened patients. Recruitment will be managed closely and if proportions of anti-AChR antibody positive or anti-AChR antibody negative (anti-MuSK or anti-LRP4 antibody-positive) exceed expected rates an operational cap may have to be introduced.

Approximately *185* patients will be enrolled during the global enrollment phase of this study.

4.1.1 Inclusion Criteria

Patients must meet the inclusion criteria below to be eligible for study entry.

- Signed Informed Consent Form
- Age ≥ 12 years *(or ≥ 18 years in France)* at time of signing Informed Consent Form
- For adolescent patients: Informed Consent Form for study participation signed by the parents or a legal guardian, and patient assent obtained, as per local requirements
- Ability to comply with the study protocol
- Confirmed diagnosis of gMG meeting the following criteria:
  - Documented history of myasthenic weakness
  - MG severity of MGFA Class II, III, or IV[2] at screening
  - The confirmation of the diagnosis has to be documented and supported by positive serologic test for one of the three antibody types: anti--AChR, anti--MuSK or anti--LRP4 at screening (antibody status must be confirmed by

[2] *Patients with MG Class IV at participating sites in France are excluded from the study.*

the central laboratory for all antibody types). *For sites in Germany and the Netherlands, confirmation of the diagnosis has to be documented and supported by pre-existing positive serologic test results for one of the three antibody types (anti-AChR, anti-MuSK, or anti-LRP4), which must have been ordered by a health care professional (HCP) for the patient as part of the patient's historical SOC.*

- A total MG-ADL score of ≥ 5 points at screening with more than 50% of this score attributed to non-ocular items
- Ongoing gMG treatment at a stable dose and not exceeding the maximum allowed doses specified in Section 4.3.2.3, as defined below:
  - For patients receiving azathioprine, treatment for at least 6 months and a dose that has been stable for at least 2 months prior to screening
  - For patients receiving other ISTs (i.e., mycophenolate mofetil, cyclosporine, tacrolimus), treatment for at least 3 months and a dose that has been stable for at least 4 weeks prior to screening
  - For patients receiving OCS, treatment for at least 3 months and a dose that has been stable for at least 4 weeks prior to screening
  - For patients receiving an AChEI, treatment with a dose that has been stable for at least 2 weeks prior to screening
- No contraindication to at least one of the rescue treatments: IVIg, PE, or high-dose corticosteroids
- For female patients of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use adequate contraception during the treatment period and for at least 3 months after the final dose of satralizumab.

  A female patient is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

  The following are examples of adequate contraceptive methods: bilateral tubal ligation; male sterilization; hormonal contraceptives; hormone-releasing intrauterine devices; copper intrauterine devices; male or female condom with or without spermicide; and cap, diaphragm, or sponge with spermicide.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception.
  If required per local guidelines or regulations, locally recognized adequate

methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

The contraception requirements specified above only relate to satralizumab and are the minimum requirements for contraception during to the study. Some of the allowed background treatments have additional contraceptive requirements, including measures for male partners participating in the study.

Please refer to the local prescribing information of the background treatment(s) for additional details on pregnancy related risks. If a patient is receiving a background therapy with specific contraceptive requirements, these additional contraceptive measures should be followed as described in the local prescribing information.

4.1.2 Exclusion Criteria

Patients who meet any of the exclusion criteria listed below will be excluded from study entry.

4.1.2.1 Exclusion Criteria Related to Myasthenia Gravis:

Patients who meet any of the following MG-related criteria will be excluded from the study:

- History of thymic cysts, thymoma, thymic carcinoma or other neoplasm of the thymus as defined by the 2015 WHO classification of tumors of the thymus (Marx et al. 2015) unless deemed cured by adequate treatment with no evidence of recurrence for ≥ 5 years before screening.
- History of thymectomy within 6 months prior to screening
- Ocular MG (MGFA Class I)
- *In France, MGFA Class IV MG at screening*
- Myasthenic crisis within the last 3 months prior to screening (MGFA Class V)
- Known disease other than gMG that would interfere with the course and conduct of the study (such as severe RA or symptomatic [overt] hyperthyroidism or hypothyroidism)

4.1.2.2 Exclusion Criteria Related to Previous or Concomitant Therapy:

Patients who meet any of the following criteria related to previous or concomitant therapies will be excluded from the study:

- Use of IVIg or subcutaneous immunoglobulin (SCIg) within 6 weeks prior to randomization/Day 1
- Use of PE within 8 weeks prior to randomization/Day 1
- Treatment with IL-6 inhibitory therapy (e.g., tocilizumab) at any time
- Treatment with total body irradiation, or bone marrow transplantation at any time

- Treatment with B and/or T cell–depleting agents (except anti-CD20 agents) including, but not limited to, inebilizumab and alemtuzumab at any time
- Treatment with anti-CD20 within 6 months prior to screening, unless CD19 counts are within normal range, as assessed by the central laboratory at screening
- Treatment with C5 complement inhibitors (e.g., eculizumab or ravulizumab) within 6 months prior to screening
- Treatment with neonatal Fc receptor antagonists within 6 months prior to screening
- Treatment with anti–B-lymphocyte stimulator monoclonal antibody (e.g., belimumab) at any time
- Treatment with cyclophosphamide IV within 6 months prior to screening
- Treatment with oral cyclophosphamide at any time
- Treatment with methotrexate within 8 weeks prior to screening
- Treatment with any investigational agent within 24 weeks prior to screening or 5 drug-elimination half-lives of the investigational drug (whichever is longer)
- Use of more than one IST (azathioprine, mycophenolate mofetil, cyclosporine A, tacrolimus) as background therapy except for the combination of an OCS with another permitted IST drug

4.1.2.3 General Safety Exclusion Criteria:

Patients who meet any of the following safety-related criteria will be excluded from the study:

- Any surgical procedure (except for non-ophthalmic minor surgeries*) within 4 weeks prior to screening
- Planned surgical procedure (except for non-ophthalmic minor surgeries*) during the study

  * Note: A minor surgical procedure is considered a procedure that requires only local anesthesia or conscious sedation (does not require general, neuraxial or regional anesthesia) and is done on an ambulatory/outpatient basis (e.g., toenail surgery, mole surgical excision, wisdom tooth extraction).

  Note: All ophthalmic surgical procedures, major or minor, including strabismus surgeries, are prohibited within 4 weeks prior to screening and should not be planned during the study.
- Evidence of progressive multifocal leukoencephalopathy
- Evidence of serious uncontrolled concomitant diseases that may preclude patient participation, such as other nervous system disease, cardiovascular disease, hematologic/hematopoiesis disease, respiratory disease, muscular disease, endocrine disease, including thyroid disease, renal/urologic disease, digestive system disease
- Congenital or acquired immunodeficiency, including HIV infection

- Active or recurrent bacterial, viral, fungal, mycobacterial infection, or other infection (excluding fungal infection of nail beds or dental caries) at baseline
- Infection requiring hospitalization or treatment with IV anti-infective agents within 4 weeks prior to baseline visit or oral anti-infective agents within 2 weeks prior to baseline visit
- Positive screening tests for hepatitis B, defined as either of the following:
    - Positive hepatitis B surface antigen [HBsAg]
    - Positive total hepatitis B core antibody [total HBcAb] confirmed by a positive viral DNA PCR
- Positive screening test for hepatitis C (defined as positive hepatitis C virus [HCV] antibody and detectable HCV RNA)

    Participants with positive HCV antibody and undetectable HCV RNA 12 weeks after HCV treatment completion are eligible to participate in the study.
- History of drug or alcohol abuse within 1 year prior to baseline
- History of diverticulitis or concurrent severe GI disorders (such as symptomatic diverticulosis) that, in the investigator's opinion, may lead to increased risk of complications such as GI perforation
- Evidence of latent or active tuberculosis (TB), excluding patients receiving chemoprophylaxis for latent TB infection

    A TB test (tuberculin skin test and/or an interferon-gamma release assay [e.g., QuantiFERON®-TB Gold In-Tube assay, T-SPOT TB assay]) should be conducted according to local guidance. If a patient is positive for latent TB, then the patient must be treated with appropriate anti-mycobacterial therapy for at least 4 weeks prior to initiating study treatment administration. Refer to Appendix 5 for details on TB screening and treatment.
- Receipt of live or live attenuated vaccine within 6 weeks prior to baseline
- History of blood donation (one unit or more), plasma donation or platelet donation within 90 days prior to screening and Day 1
- History of malignancy within the last 5 years, including solid tumors, hematologic malignancies and in situ carcinoma (except basal cell and squamous cell carcinomas of the skin, or in situ carcinoma of the cervix uteri that have been completely excised and cured)
- History of severe allergic reaction to a biologic agent (e.g., shock, anaphylactic reactions)
- Active suicidal ideation within 6 months prior to screening or history of suicide attempt within 3 years prior to screening
- Any serious medical condition or abnormality in clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study

- Pregnant or breastfeeding, or intending to become pregnant during the study or within 3 months after the final dose of satralizumab

  Female patients of childbearing potential must have a negative serum pregnancy test result at screening prior to initiation of study drug.

4.1.2.4 Laboratory Exclusion Criteria (at Screening):

Patients who have any of the following laboratory abnormalities at screening will be excluded from the study:

- WBC $< 3.0 \times 10^3/\mu L$
- ANC $< 2.0 \times 10^3/\mu L$
- Absolute lymphocyte count $< 0.5 \times 10^3/\mu L$
- Platelet count $< 10 \times 10^4/\mu L$
- AST or ALT $> 1.5 \times$ upper limit of normal (ULN)

If retest is conducted because the initial result meets an exclusion criterion, it must be conducted at a central laboratory and the last value obtained determines the patient's eligibility for randomization/*Day 1*, otherwise local laboratory can be used.

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

Randomization and blinding will be employed to minimize bias in treatment assignment *in the DB period* and to provide the basis for valid statistical inference.

4.2.1 Treatment Assignment

This is a randomized, DB study *(except for adolescent patients enrolled directly in the OLE period of the study)*. After initial written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a patient, the study site will obtain the patient's identification number and treatment kit assignment from an interactive voice or web-based response system (IxRS).

Patients will be randomly assigned to one of two treatment groups: placebo or satralizumab. Eligible patients must be randomized through the IxRS prior to receiving any study drug. Randomization will occur in a 1:1 ratio through use of a permuted-block randomization method to ensure a balanced assignment to each treatment group. Randomization will be stratified according to the following criteria:

- Baseline SOC treatment: AChEI monotherapy and/or an OCS versus a steroid-sparing IST monotherapy or a combination of steroid-sparing IST with other treatments (an AChEI and/or an OCS)
- Autoantibody type: AChR positive versus AChR negative (includes MuSK gMG and LRP4 gMG)
- Region: North America versus Europe versus rest of world

Adolescent patients enrolled in the study will directly enter the OLE period after completion of screening and receive open-label satralizumab. For information on adolescents that have been enrolled through previous versions of the protocol (prior to global protocol Version 5), refer to Section 3.1.3.

The IxRS system will also take into account patients' weight at baseline to allocate to the correct dose.

4.2.2 Blinding

Study site personnel and patients will be blinded to treatment assignment during the study. The Sponsor and its agents will also be blinded to treatment assignment, with the exception of individuals who require access to patient treatment assignments to fulfill their job roles during a clinical trial. These roles include the unblinding group responsible, clinical supply chain managers, central laboratory sample handling staff, operational assay group personnel, IxRS service provider, and iDMC members.

To maintain integrity of the trial results and to prevent potential unblinding of the assigned group during the DB treatment phase as a result of adverse events or changes to laboratory results, the following additional measures will be implemented until the time of the primary analysis:

- To prevent potential unblinding as a result of adverse events or laboratory changes, a "**dual assessor**" approach will be used to evaluate efficacy and safety. Each site will have two separate investigators: a treating investigator and a rating or examining investigator.

  The **treating investigator** will be the safety assessor and should be a neurologist with experience in the care of patients with MG. The Treating Investigator will have access to all patient data and will make all treatment decisions on the basis of a patient's clinical response and laboratory findings. This role may be conducted by the principal investigator.

  The **examining investigator** will be the efficacy assessor and should be a qualified HCP trained and experienced in administering and scoring the MG-ADL, QMG, and MGC. The examining investigator (or designee, fulfilling the same criteria) will complete the QMG and MGC assessments. During the DB treatment period, the examining investigator and his or her qualified designees (if applicable) will not be involved with any aspect of medical management of the patient and will not be allowed access to patient data. The roles of the treating and examining investigator need to be documented in the Investigator's Site File for each patient. The treating investigator and the examining investigator should not switch roles for a specific patient. It is recommended that the same examining investigator assesses a specific patient throughout the DB treatment period. This role cannot be conducted by the principal investigator.

  The dual assessor approach should be applied until the database lock for the primary analysis for the study has been achieved.

- Patient education: During the DB treatment period, prior to being examined by the examining investigator, patients should be instructed not to discuss with the examining investigator what (if any) adverse effects they may be experiencing.
- Blinding of laboratory parameters: Selected laboratory parameters that may lead to unblinding of the treatment assignment, such as fibrinogen, CRP, immunoglobulins, and complement levels, will be blinded until the primary analysis is complete. The iDMC will perform periodic unblinded safety reviews, which include the blinded laboratory parameters.

While PK and immunogenicity samples must be collected from patients assigned to the placebo group to maintain the blinding of treatment assignment, PK and ADA assay results for these patients are generally not needed for the safe conduct or proper interpretation of the study data. Laboratories responsible for performing study drug PK and ADA assays will be unblinded to patient treatment assignments to identify appropriate samples for analysis. PK samples from patients assigned to the placebo group will not be analyzed for study drug PK concentration except by request (e.g., to evaluate a possible error in dosing). Baseline immunogenicity samples will be analyzed for all patients. Post-baseline immunogenicity samples from patients assigned to the placebo group will not be analyzed for ADAs except by request.

If unblinding is necessary for a medical emergency (e.g., in the case of a serious adverse event for which patient management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by contacting the IxRS. The treatment code should not be broken except in emergency situations. The investigator is not required to contact the Medical Monitor prior to breaking the treatment code. *However, the investigator should inform the Medical Monitor that the treatment code has been broken.*

If the investigator wishes to know the identity of the study drug for any reason other than a medical emergency, he or she should contact the Medical Monitor directly. The investigator should document and provide an explanation for any non-emergency unblinding. If the Medical Monitor agrees to patient unblinding, the investigator will be able to break the treatment code by contacting the IxRS.

As per health authority reporting requirements, the Sponsor's Drug Safety representative will break the treatment code for all serious, unexpected suspected adverse reactions (see Section 5.7) that are considered by the investigator or Sponsor to be related to study drug. The patient may continue to receive treatment, and the investigator, patient, and Sponsor personnel, with the exception of the drug safety representative and personnel who must have access to patient treatment assignments to fulfill their roles (as defined above) will remain blinded to treatment assignment.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal product (IMP) for this study is satralizumab. Background therapy and rescue therapy are considered *auxiliary medicinal products (AxMPs). Appendix 15 identifies all IMPs and AxMPs for this study (for use in European Economic Area [EEA]).*

In this protocol, "study treatment" refers to satralizumab or placebo (assigned in addition to background therapy).

4.3.1 Study Treatment Formulation and Packaging

4.3.1.1 Satralizumab and Placebo

IMP will be supplied by the Sponsor as prefilled syringe (PFS) assembled with a plunger rod, needle safety device (NSD), and extended finger flange (EFF) filled with 1.0 mL of solution for SC injection corresponding to 120 mg satralizumab. Satralizumab placebo PFS is identical in composition to satralizumab PFS, but does not contain the satralizumab active ingredient. It will be identical in appearance and packaging to satralizumab. A PFS (assembled with an NSD/EFF) filled with 0.5 mL of solution, corresponding to 60 mg satralizumab, will be used in the OLE period (after the second OLE dose) once it becomes available at the study site.

For information on the formulation and handling of satralizumab, see the pharmacy manual.

4.3.1.2 Background Therapy

Oral Corticosteroids

For information on the formulation and packaging of OCSs, see the local prescribing information for OCSs.

Immunosuppressive Therapy

For information on the formulation and packaging of azathioprine, mycophenolate mofetil, cyclosporine A, tacrolimus, see the local prescribing information for the respective treatment.

Acetylcholinesterase Inhibitors

For information on the formulation and packaging of AChEI (pyridostigmine, neostigmine, ambenonium), see the local prescribing information.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1.

Details on treatment administration (e.g., dose and timing) should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental

overdose, medication error, drug abuse, or drug misuse, along with any associated adverse events, should be reported as described in Section 5.3.5.12.

Guidelines for treatment interruption or discontinuation for patients who experience adverse events are provided in Section 5.1.4.1.

4.3.2.1 Satralizumab and Placebo

Patients will receive satralizumab or placebo at Weeks 0, 2, 4 (loading doses) and maintenance doses Q4W thereafter during the DB period. Patients will receive the second and the third loading dose (administered at Weeks 2 and 4) within a ± 3-day window for both dosing visits and all subsequent doses within a ± 7-day window for each dosing visit. The minimal dosing interval between two loading doses is 8 days. It should be noted that the second loading dose and the Week 2 assessments should coincide and occur 14 (±3) days after Study Day 1.

Study drug will be administered by SC injection in the abdominal or femoral region by the investigator or designated person after all other study-related procedures have been performed at a site visit. For the first 5 doses of study drug in the DB and OLE periods, all patients should be observed for the signs and symptoms of hypersensitivity reactions at the study site for at least 1 hour after administration of study treatment.

In case of disease exacerbation that requires rescue therapy, study drug administration will be continued as scheduled, concurrently with rescue therapy, unless the investigator considers it necessary to discontinue study treatment. Patients who receive PE as rescue therapy will receive loading doses of study drug as soon as possible post-PE.

The dose of study treatment will be determined on the basis of body weight.
Patients with a body weight ≤ 100 kg will receive 120 mg SC satralizumab or the matching volume of placebo. Patients with a body weight > 100 kg will receive 180 mg SC satralizumab or the matching volume of placebo, given as two injections (one 1-mL PFS, and one additional 0.5-mL injection).

An interim PK analysis *was* included to confirm that the achieved exposures are within the target range (see Section 6.11.2). Based on the results of this analysis and pre-specified criteria, the dosing regimen *could* be modified from 120 mg to 180 mg and from 180 mg to 240 mg for patients ≤ 100 kg and > 100 kg, respectively, if needed to achieve target concentrations. *For further details on the interim analysis, see Section 6.11.2.*

For preparation and administration of the 180-mg or 240-mg doses of study drug (in case of dose modification), please refer to the pharmacy manual.

In the OLE period, all patients can receive open-label treatment with satralizumab, as determined on the basis of body weight, as described above. *Adult and adolescent* patients who receive active treatment during the DB period (Group A) will continue to

receive OLE satralizumab subcutaneously Q4W, with a dose of placebo administered at Week 2 of the OLE period in order to maintain blinding to DB treatment assignment. *Adult and adolescent* patients who receive placebo treatment during the DB period (Group B) will be administered loading doses of satralizumab subcutaneously at Weeks 0, 2, 4, and maintenance doses Q4W thereafter of the OLE period. After Week 24 of the OLE period and in accordance with local regulations, administration of satralizumab outside of the study site (e.g., mobile nursing by a qualified HCP or home treatment [self-administration or administration by a trained caregiver]) may be allowed on scheduled study drug administration days if no on-site assessments are scheduled for that dosing date (see Appendix 2). The investigator will assess if it is appropriate for a given patient to receive study drug by self-administration or administration by a caregiver outside of the study site. If administration outside the study site is appropriate, patients will be required to give written informed consent to participate in mobile nursing visits or home treatment. Patients and their caregivers will be provided with emergency contact information by the site.

Adolescent patients enrolled directly in the OLE period will receive satralizumab treatment at Weeks 0, 2, and 4 (loading doses) and maintenance doses Q4W thereafter. Patients will receive the second and the third loading dose (administered at Weeks 2 and 4) within a ±3-day window for both dosing visits and all subsequent doses within a ±7-day window for each dosing visit. The minimal dosing interval between two loading doses is 8 days. It should be noted that the second loading dose and the Week 2 assessments should coincide and occur 14 (±3) days after Study Day 1.

If eligible for and willing to participate in self-administration, patients and their caregivers will be trained how to administer study drug. After the patient or caregiver signs the Informed Consent for Optional Home Treatment, training of the patient or caregiver can begin from the Week 16 OLE visit and should continue until the patient or caregiver has demonstrated competence in administering the injection of the study drug correctly. The assessment to determine the patient's or caregiver's competence in performing the injection needs to be made by the Principal Investigator (or delegate) and should be documented in the patient's medical records. After the patient or the patient's caregiver has demonstrated competence in giving the injection correctly, SC injections may be administered by the patient or the patient's caregiver at home. Patients should be followed up by the study site personnel through phone calls around the scheduled study drug administration dates to monitor compliance, concomitant medications, and adverse events. If a patient is unable or does not wish to administer study drug at home, clinic staff will continue to administer injections to the patient at the study site.

Patients and their caregivers will be instructed in how to recognize any signs and symptoms of hypersensitivity reaction and to identify when to seek emergency medical care in case of an extreme reaction. Patients will record details of their home -administered study drug injections in a diary. Site personnel will monitor the study medication records from the diary at the in-clinic visits. An HCP who is trained on

study drug preparation, storage and administration should perform the preparation and SC administration of any dose that is not in a form of PFS.

Refer to the pharmacy manual for detailed instructions on drug storage, and administration.

4.3.2.2 Modifications of Dose or Treatment Schedule

In the event that an enrolled patient gains or loses weight during the study such that they would fall into a different dosing band, the following instructions apply (see Table 6)

Table 6 Dosing Regimen Switches for Patients Who May Lose or Gain Body Weight

Body Weight at Baseline	Dosing Regimen Switches
≤ 100 kg	Increase dose of study drug to higher dose (180 mg) if a patient's weight increases to ≥ 105 kg, confirmed at two consecutive measurements minimum 6 weeks apart
> 100 kg	Reduce dose of study drug to 120 mg if a patient's weight decreases to ≤ 95 kg, confirmed at two consecutive measurements minimum 6 weeks apart

The dosage may be modified based on the results of the interim PK analysis (see Section 6.11.2).

Delayed Dosing Visits and Missed Doses

Delayed dosing visits may be scheduled if the study drug cannot be administered at the timepoints defined in the schedule of activities (see Appendix 1 and Appendix 2).

Thus, a patient who has all assessments of a dosing visit performed but could not receive his or her dose of study drug, should be rescheduled for the SC drug administration. At the delayed dosing visit, minimum safety pre-dosing assessments, including physical examination and vital signs measurements, ECG, PK, PD, and ADA sampling and study drug administration will be performed. Other pre-dosing assessments are listed in the schedule of activities. Additional tests or assessments, such as routine safety laboratory tests, may be performed when the investigator judges that these are warranted, and should be recorded in the CRF.

Patients with active infection during the study should be promptly evaluated and treated appropriately; study drug injection should be delayed until the infection is controlled. For serious infections or Grade ≥ 3 infections, study drug injection should be delayed until the infection has completely resolved.

If a patient cannot come to the site for a scheduled visit, every effort should be made to collect all the missing data. Additionally, the site staff should follow up with patients

around the time of the scheduled visit by telephone to collect any information on safety and/or neurological worsening the patient might experience.

If study drug cannot be administered within the scheduled visit window and is subsequently administered outside the visit window, the next dose of study drug should be administered on schedule (minimum dosing interval should be 8 days (for loading dose) and 14 days (for maintenance dose).

Site staff should consult with the Medical Monitor if in doubt as to how to schedule dosing in such circumstances.

Missed Doses

If the delay in dosing is such that the minimum allowable interval between doses cannot be maintained within the acceptable dosing windows defined, or dosing cannot be completed prior to the date of the next planned dose, then the dose is considered to have been missed. If a study drug injection is missed, it should be administered as described in Table 7 provided there are no safety-related reasons for further interruption or discontinuation of study treatment (see Section 5.1).

Table 7 Recommended Dosage for Delayed or Missed Doses and after Rescue Therapy with Plasma Exchange

Last Dose Administered	Recommended Dosage for Delayed or Missed Doses
Less than 8 weeks during the maintenance period or missed a loading dose	Administer study drug by SC injection as soon as possible. If the delayed dosing falls within the next visit window, no delayed dosing visit entry needs to be recorded on the eCRF. The site should enter data for all assessments and study drug administration on the next scheduled visit eCRF page. <u>Loading period</u> • If the second loading dose (Week 2 of DB period or Week 2 of OLE period) is delayed or missed, administer dose as soon as possible and administer the third and final loading dose 14 (±3) days later. The minimal dosing interval between the second and the third loading dose is 8 days. • If the third loading dose (Week 4 of DB or Week 4 of OLE period) is delayed or missed, administer dose as soon as possible and administer the next dose 4 weeks (±7 days) later.
weeks to less than 12 weeks	Administer study drug by SC injection at 0 [a] and 2 weeks (±3 days), followed by administration every 4 weeks (±7 days). The assessments specified for RLDs 1 and 2 should be completed. Study assessments should then resume as per the schedule of activities (see Appendix 1 and Appendix 2)
12 weeks or longer or After rescue therapy with PE	Administer study drug by SC injection at 0 [a], 2 weeks (±3 days), and 4 weeks (±3 days) followed by administration every 4 weeks (±7 days) (*For treatment interruptions of ≥12 weeks, during which safety assessments have not been conducted, at RLD 1 visit it is recommended to perform a laboratory assessment and review of the safety labs including LFTs [Table 8], ANC [Table 9] and platelets [Table 10] prior to administering study drug. Patients should be carefully examined for any signs of active infection and if required, additional tests should be performed at the discretion of the principal investigator prior to study drug administration).* The assessments specified for RLDs 1, 2, and 3 *Visits are to* be completed. Study assessments should then resume as per the schedule of activities (see Appendix 1 and Appendix 2).

ANC = absolute neutrophil count; DB = double-blind; eCRF = electronic Case Report Form; *LFT = liver function test*; OLE = open-label extension, PE = plasma exchange; *RLD = re-loading dose*

[a] "0 weeks" refers to time of the first administration after the missed dose.

Site staff should discuss with the Medical Monitor how to schedule dosing in such circumstances.

4.3.2.3 Background Therapy

In the DB period (in addition to satralizumab or placebo) patients will receive background treatment with OCSs and/or IST and/or AChEIs at a stable dose not exceeding the following doses:

- Azathioprine: 3 mg/kg/day for adults, 2.5 mg/kg/day for adolescents (O'Connell et al. 2020)
- Mycophenolate mofetil: 3000 mg/day for adults, 2000 mg/day for adolescents
- Cyclosporin A: 5 mg/kg/day
- Tacrolimus: 0.2 mg/kg/day for adults, 0.1 mg/kg/day for adolescents (Ponseti et al. 2008)
- Oral glucocorticoids: 30 mg/day (prednisone equivalent)
- Pyridostigmine: 600 mg/day for adults, up to 1.5 mg/kg 5 times per day for adolescents (maximum 450 mg/day) (O'Connell et al. 2020)
- Neostigmine: 375 mg/day
- Ambenonium: 300 mg/day

These are considered *AxMPs (for use in the EEA), see Appendix 15*.

In addition to OCSs, only one IST or immunomodulatory drug at a stable dose is allowed during the DB period (see Section 4.1.1).

AChEIs **should not be taken for 10 hours prior** to completion of efficacy assessments including QMG and MGC testing at each study visit (except screening visit) if medically safe to do so.

In the DB period and the first 12 weeks of the OLE period a dose decrease of baseline treatments is permitted only for safety reasons. Dose increase or change of background treatment is strongly discouraged.

In the OLE period, background treatment, for all *adult and adolescent* patients *randomized in the DB period at the start of the study*, should be maintained stable for at least the first 12 weeks to allow satralizumab levels to reach steady state in the patients who received placebo during the DB period. Patients can be tapered off steroids, ISTs, and AChEIs after Week 12 of the OLE period based on the investigator's judgment.

For adolescent patients enrolled directly into the OLE, stable background therapy should be maintained until Week 24 of the OLE period (see Section 3.1.3).

4.3.3 Rescue Medication

Patients may receive rescue therapy in case of MG clinical deterioration/exacerbation on any study day. Exacerbation of MG is defined in Section 3.1.4.

Rescue therapy includes IVIg (2 g/kg administered over a 2- to 5- day period), or PE with or without high-dose corticosteroids (500–1000 mg/day IV methylprednisolone or equivalent for 2–5 days). High-dose corticosteroid therapy should always be administered in combination with IVIg or PE.

The choice of rescue therapy will be determined by the investigator on the basis of his or her overall clinical assessment.

Study drug administration will be continued as scheduled, concurrently with rescue therapy, unless the investigator considers it necessary to discontinue study treatment.

Patients who receive PE as rescue therapy will receive re-loading doses of study drug as soon as possible post-PE (see Section 4.3.2.2, Table 7).

All efforts should be made by the investigator to keep patients in the study during the DB period and continue study drug administration even after experiencing a MG exacerbation requiring rescue therapy.

4.3.4 Investigational Medicinal Product Handling and Accountability

All IMPs required for completion of this study will be provided by the Sponsor. The study site (i.e., investigator or other authorized personnel [e.g., pharmacist or mobile nurse]) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each patient, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that patients are provided with doses specified by the protocol.

The study site should follow all instructions included with each shipment of IMP. The study site will acknowledge receipt of IMPs supplied by the Sponsor using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced. The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit*, either by time monitoring (shipment arrival date and time) or temperature monitoring,* for all IMPs received and that any discrepancies have been reported and resolved before use of the IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.

Only patients enrolled in the study may receive IMPs.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the drug accountability log.

Refer to the pharmacy manual and/or the Satralizumab Investigator's Brochure for information on IMP handling, including preparation and storage, and accountability.

4.3.5 Continued Access to Satralizumab

The Sponsor will offer continued access to Roche IMP satralizumab free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive Roche IMP satralizumab after completing the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued Roche IMP treatment for his or her well-being.
- There are no appropriate alternative treatments available to the patient.
- The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them.

A patient will not be eligible to receive Roche IMP satralizumab after completing the study if any of the following conditions are met:

- The Roche IMP is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient).
- The Sponsor has discontinued development of the IMP or data suggest that the IMP is not effective for gMG.
- The Sponsor has reasonable safety concerns regarding the IMP as treatment for gMG.
- Provision of the Roche IMP is not permitted under the laws and regulations of the patient's country.

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following website:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

Patients may be eligible to receive satralizumab as part of an OLE study, as described in Section 3.1.2.

4.4 CONCOMITANT THERAPY, PROHIBITED FOOD, AND ADDITIONAL RESTRICTIONS

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from screening visit to end of study visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

The Medical Monitor may be consulted if there are any questions related to concomitant or prior therapy.

4.4.1 Permitted Therapy

Patients are permitted to use the following therapies during the study:

- Oral contraceptives (see Section 4.1.1)
- Hormone-replacement therapy
- Background treatment with any of the drugs listed in Section 4.3.2.3

  The dose must not exceed the dose defined in Section 4.3.2.3. In the DB period, a dose decrease of baseline treatments is permitted only for safety reasons. Dose increase or change of background treatment is strongly discouraged.
- Rescue therapy in case of acute MG exacerbation defined as IVIg and/or PE administered with or without pulse IV corticosteroids (see Section 4.3.3)

  The choice of rescue therapy will be determined by the investigator on the basis of his or her overall clinical assessment.

  Study drug administration will be continued as scheduled, concurrently with rescue therapy, unless the investigator considers it necessary to discontinue study treatment.
- Treatment with topical (e.g., ophthalmic, nasal, otic, cutaneous) corticosteroids for adverse events (i.e., indications other than background MG therapy), provided that the duration of treatment is kept as short as possible.
- Pain medications (including topical agents, antiepileptic drugs [e.g., pregabalin, gabapentin, carbamazepine], antidepressants [tricyclic antidepressants and serotonin norepinephrine reuptake inhibitors, e.g., duloxetine], and non-opioid analgesics [e.g., acetaminophen, non-steroidal anti-inflammatory drugs]).

4.4.2 Cautionary Therapy

Medications that have the strongest evidence for worsening MG should be avoided (Sanders et al. 2016; Myasthenia Gravis Foundation 2020) and include the following:

- Magnesium: potentially dangerous if given intravenously, i.e., for eclampsia during late pregnancy or for hypomagnesemia. Use only if absolutely necessary and observe for worsening.
- Macrolide antibiotics (e.g., erythromycin, azithromycin, clarithromycin): commonly prescribed antibiotics for gram-positive bacterial infections. Use cautiously, if at all.
- Aminoglycoside antibiotics (e.g., gentamycin, neomycin, tobramycin): used for gram-negative bacterial infections. Use cautiously if no alternative treatment available.
- Procainamide: used for irregular heart rhythm. Use with caution.
- Desferrioxamine: a chelating agent used for hemochromatosis.
- β-blockers: commonly prescribed for hypertension, heart disease and migraine headaches but potentially dangerous in MG. May worsen MG. Use cautiously.
- Statins (e.g., atorvastatin, pravastatin, rosuvastatin, simvastatin): used to reduce serum cholesterol. Statins may worsen or precipitate MG. Use cautiously if indicated and at the lowest dose needed.
- Iodinated radiologic contrast agents: older reports document increased MG weakness, but modern contrast agents appear to be safer. Use cautiously and observe for worsening.
- In addition, all drugs that are respiratory depressants (e.g., benzodiazepines, opioids, sedatives) should be used with caution.

The use of cautionary therapies defined above must be recorded on the eCRF. Adverse events related to the administration of these therapies must be documented on the appropriate eCRF.

4.4.2.1 Medications Given with Precaution due to Effects Related to CYP Enzymes

No drug-drug interaction studies have been performed. Pop PK analyses did not detect any effect of azathioprine, mycophenolate mofetil, or OCS on the clearance of satralizumab.

Both in vitro and in vivo studies have shown that the expression of specific hepatic CYP450 enzymes (CYP1A2, CYP2C9, CYP2C19, and CYP3A4) is suppressed by cytokines such as IL-6. Modestly elevated IL-6 levels have been reported in patients with gMG.

Caution should be exercised when starting or discontinuing satralizumab treatment in patients who are receiving substrates of CYP450 3A4, 1A2, 2C9 or 2C19, particularly those with a narrow therapeutic index (such as warfarin, carbamazepine, phenytoin, and theophylline), and/or background ISTs (including tacrolimus and cyclosporine) and doses adjusted if needed.

Given the prolonged terminal half-life of satralizumab (approximately 30 days), the effect of satralizumab may persist for several months after stopping therapy.

The above lists of medications are not necessarily comprehensive. The investigator should consult the prescribing information when determining whether a concomitant medication can be safely administered with study treatment. In addition, the investigator should contact the Medical Monitor if questions arise regarding medications not listed above.

4.4.3 Prohibited Therapy

Use of the following concomitant therapies is prohibited during the study as described below:

- Use of chronic IVIg (defined as more than 2 consecutive treatments administered at 4- to 6-week intervals) or chronic SCIg during the study
- Use of chronic PE (more than two treatment cycles performed at 4- to 8-week intervals) during the study
- Treatment with alternative IL-6/ IL-6-R inhibitory therapy (e.g., tocilizumab)
- Treatment with total body irradiation, or bone marrow transplantation
- Treatment with B- and/or T-cell depleting agents including but not limited to rituximab, inebilizumab and alemtuzumab
- Treatment with complement inhibitors (e.g., eculizumab), neonatal Fc receptor antagonists, or anti–B-lymphocyte stimulator monoclonal antibody (e.g., belimumab)
- ISTs except for background therapy permitted per protocol (i.e., OCSs, azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus)
- Antibiotics telithromycin and fluoroquinolones (e.g., ciprofloxacin, moxifloxacin and levofloxacin)
- Botulinum toxin
- D-penicillamine
- Quinine (e.g., chloroquine)
- Treatment with any investigational agent within 24 weeks prior to screening or 5 drug-elimination half-lives of the investigational drug (whichever is longer) and until the end of the study
- Immunization with live or live attenuated vaccine within 6 weeks prior to baseline and until the end of the study
- Chinese herbal medicine preparations

Participants who receive any of these prohibited therapies may be required to permanently discontinue study treatment (see Section 4.6.1). The Medical Monitor should be contacted to discuss permanent discontinuation of study treatment.

The use of prohibited therapies defined above must be recorded on the eCRF. Adverse events related to the administration of these therapies must be documented on the appropriate eCRF.

4.4.4 Additional Restrictions

AChEIs **should not be taken for 10 hours prior** to completion of efficacy assessments including QMG and MGC testing at each study visit (except screening visit) if medically safe to do so.

4.4.5 Immunizations and Vaccinations

It is recommended for all patients to keep up to date with all immunizations according to local immunization guidelines prior to randomization/*Day 1* in the study.

- The use of any live and live attenuated vaccines is not allowed within 6 weeks prior to randomization/*Day 1* and during the entire duration of the study.
- Vaccines (including COVID-19 vaccines) other than live or live attenuated are permitted during the study. Vaccines may be less effective in immunocompromised patients, however, the effect of satralizumab upon the efficacy of vaccinations is currently unknown. It is recommended that vaccines should be given in accordance with the approved/authorized vaccine label and official local immunization guidance.

Refer to the current Satralizumab Investigator's Brochure for further details regarding vaccinations.

Please contact the Medical Monitor for questions on vaccinations in patients participating in this study.

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1 (DB period) and Appendix 2 (OLE period). All activities should be performed and documented for each patient.

Patients will be closely monitored for safety and tolerability throughout the study. Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and local laboratory test values are acceptable.

At applicable sites, certain study assessments, including study drug administration, may be performed by a mobile nurse (MN) professional at the patient's home or another suitable location, to improve access and convenience for patients participating in the study. The Sponsor will select a healthcare company that will be responsible for providing MN services for participating sites (the MN vendor). The MN vendor is responsible for ensuring that all MN professionals are licensed, qualified, and in good standing, as per applicable regulations, and that appropriate background checks have been performed. If the investigator at a participating site determines that MN services are appropriate for a patient and the patient gives written informed consent to participate

in MN visits, the MN network will communicate with the patient and the patient's site. MN visits will be scheduled on specified visit days, to allow for relevant assessments to be performed by the MN professional. The schedule of activities (see Appendix 1 and Appendix 2) will specify the assessments that may be performed by an MN professional.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before randomization/*Day 1*. The investigator will maintain a detailed record of all patients screened and to document eligibility or record reasons for screening failure, as applicable.

4.5.2 Screening Assessments

Once informed consent is obtained, screening assessments can occur. Screening tests and evaluations will be performed within 28 days prior to Day 1, unless otherwise specified. The 28-day screening period may be extended, in exceptional circumstances, but cannot exceed 42 days. If the screening period is extended, the safety laboratory assessments specified in Section 4.1.2.4 must be completed within 28 days prior to randomization/Day 1.

If a patient does not meet any laboratory inclusion or exclusion criteria at screening, the test can be repeated within 42 days of screening (i.e., retest). A retest is defined as any assessment repeated within 42 days of screening.

If a patient has not met all of the inclusion/exclusion criteria within 42 days (screen failure) of the original screening visit, re-screening (which refers to repeating the whole screening process) can be conducted once. Each patient must be re-consented before re-screening occurs. As part of the re-screening process, a TB test and hepatitis tests, MG autoantibody (AChR, MuSK, LRP4 serotype confirmation by the central laboratory) testing[3] are not required if each of them is conducted within 12 weeks prior to baseline.

Screen failures are defined as patients who sign the Informed Consent Form but are not subsequently *enrolled*. If a patient is a considered a screen failure, the investigator will maintain a record of reasons for screen failure.

If a patient experiences myasthenic crisis during the screening period, the patient should be treated as a screen failure and should receive rescue medication as outlined in

[3] *For sites in the Netherlands and Germany, the central laboratory autoantibody tests at screening to confirm gMG diagnosis is not required.*

Section 4.3.3. The patient can be re-screened and must re-sign the Informed Consent Form.

Please see Appendix 1 for the schedule of screening assessments *for adult and adolescent patients who enter the DB period and Appendix 2 for adolescent patients who enter directly in the OLE period.*

4.5.2.1 Hepatitis B Screening

Patients who are HBsAg positive will be excluded from the study.

If total HBcAb status is positive, hepatitis B virus (HBV) DNA will be measured at a central laboratory. If HBV DNA is undetectable, the patient may be enrolled. In these cases, HBV DNA measurements must be performed regularly at approximately 12-weekly intervals during the study. If HBV DNA is detectable, the patient must be excluded.

4.5.2.2 Hepatitis C Screening

Patients with negative hepatitis C serology can be enrolled. Patients with positive hepatitis C serology will be excluded from the study. However, if HCV RNA is undetectable ≥ 12 weeks after HCV treatment completion, the patient can be enrolled.

4.5.2.3 Screening for Tuberculosis

For entry into this study, patients should be screened for TB at the site according to the instruction for TB screening (see Appendix 5). The results of the screening tests will be reported on the eCRF. If the patient is positive for latent TB, appropriate anti-mycobacterial therapy must be administered for at least 4 weeks before initiating study drug administration in this study. For further details on screening for TB, see Appendix 5.

4.5.3 Medical History, Baseline Conditions, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, and use of alcohol and drugs of abuse, will be recorded at baseline. The investigator will record on the eCRF:

- The date of MG diagnosis,
- Diagnostic criteria used to establish the diagnosis of gMG (clinical presentation, autoantibody presence, abnormal neuromuscular transmission demonstrated by either single-fiber electromyography or repetitive nerve stimulation, positive edrophonium chloride test result, response to AChEI),
- Antibody type, titer levels, and the date of testing
- MGFA Class at time of diagnosis and at time of screening
- History of thymectomy with the date of the procedure

- History of MG exacerbations and crisis
- History of IST/immunomodulatory therapy use (including anti-CD20 agents, complement inhibitors, acute and maintenance IVIg, and PE therapies), inclusive of drug name, prescribed maximum dose, treatment duration, and reason for treatment failure
- History of refractory MG defined as:
  - A failure to respond to treatment with OCS and two or more immunosuppressive/immunomodulatory therapies either in combination or as monotherapy, used in adequate doses for an adequate duration, with persistent symptoms or side effects that limit functioning, as defined by patient and physician **for AChR+ and LRP4+ patients** (Sanders et al. 2016).
  - A failure to respond to rituximab used as a monotherapy or in combination with OCS after more than 6 months. Treatment failure is defined either by persistent symptoms or side effects that limit functioning, as defined by patient and physician **for MuSK+ patients**.
- History of any hospital admissions for MG since diagnosis and within the last 2 years
- All medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient from screening

At the time of each follow-up physical examination, adverse events and any changes in medications and allergies should be recorded.

Demographic data will include age, sex, and self-reported race/ethnicity.

4.5.4 Physical Examinations

A complete physical examination, performed at screening and other specified visits, should include an evaluation of the head, eyes, ears, nose, and throat, cardiovascular, respiratory, GI, dermatologic, musculoskeletal, and neurologic systems; genitourinary examinations may be performed if clinically indicated. The neurologic examination, performed as part of the complete physical examination, should include an assessment of the mental status, cranial nerve function, motor function, sensory function, reflexes, coordination, and gait. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

Limited, symptom-directed physical examinations should be performed at specified post-baseline visits and as clinically indicated. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.5 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, body temperature, and systolic and diastolic blood pressure while the patient is in a seated position. Vital

signs will be measured just before dosing and 15 (±5) minutes and 60 (±5) minutes after dosing during the first five dosing visits of the DB, and OLE periods (i.e., if no missed doses, Week 0 to Week 12 of the DB and Week 0 to Week 12 of the OLE). After the fifth study drug dose, vital signs should be measured only before study drug administration.

Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).

Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

4.5.6 Laboratory, Biomarker, and Other Biological Samples

Samples for the following laboratory tests will be sent to the central laboratory for analysis. Instruction manuals and supply kits will be provided for all central laboratory assessments.

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and absolute differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)
- Coagulation: INR and fibrinogen
- Serum chemistry: sodium, potassium, chloride, calcium, phosphorous, ferritin, BUN, creatinine, total bilirubin, total protein, albumin, ALT, AST, ALP, gamma-glutamyl transpeptidase, lactate dehydrogenase, CRP, CK, lipase, and uric acid
- Lipids: total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides
- Quantitative immunoglobulins: IgA, IgG, IgM, and IgE
- IgG subclass (IgG1, IgG2, IgG3 and IgG4)
- T-, B- (defined by CD19+) and natural killer cells (TBNK panel)
- Complement C3, C4 and CH50
- Screening for HBV infection: HBsAg, total HBcAb, and (if HBsAg test is negative and total HBcAb test is positive) HBV DNA.
- Screening for HCV infection: HCV antibody and (if HCV antibody test is positive) HCV RNA. If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an HCV infection.
- Serum pregnancy test at screening

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

- Urinalysis (urinary glucose, urinary protein, urinary occult blood, urobilinogen) will be conducted at each site by dipstick. If any abnormalities are detected on urine

dipstick tests, a complete urinalysis (including microscopic of examination of urine) and/or urine culture is to be performed (at local laboratory) as deemed necessary.

- Interferon Gamma Release Assay as part of TB screening
- Cortisol and low-dose ACTH stimulation test (if deemed necessary after Week 12 of the OLE period)
- Pregnancy test:

  All female patients of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test done centrally at the screening visit. During the study, serum or urine pregnancy tests will be performed at the study site at subsequent visits. For adolescent patients at the time of informed consent, urine β-human chorionic gonadotropin will be recommended during the study except screening in order to reduce the blood volume taken. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

  A female patient is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.

The following samples will be sent to the Sponsor or a designee for analysis:

- PK/PD assessments: serum samples for satralizumab concentration, IL-6, and sIL-6R
- Immunogenicity assessments: serum sample for ADA analysis
- Serum samples for determination of autoantibodies at screening, e.g., anti-AChR, anti-MuSK, and anti-LRP4 [4]
- Serum, plasma, blood, and peripheral blood mononuclear cells (PBMCs) samples for exploratory research on biomarkers potentially related to disease, drug, or clinical response and biomarker assay development

Exploratory biomarker research may include, but will not be limited to, the following:

- gMG-associated autoantibodies during the DB and OLE periods (e.g., anti-AChR, anti-MuSK, and anti-LRP4)
- Biomarkers associated with inflammation and T- and B-cell function (e.g., IL-17 and B-cell subsets)
- Live-cell assays in PBMCs, e.g., T- and B-cell activation and proliferation

Research may involve extraction of DNA or RNA; analysis of mutations, single nucleotide polymorphisms, and other genomic variants; and genomic profiling through

[4] *For sites in the Netherlands and Germany, the central laboratory autoantibody tests at screening to confirm gMG diagnosis are not required.*

use of next-generation sequencing (NGS) of a comprehensive panel of genes. Genomic research will be aimed at exploring inherited characteristics. NGS methods may include whole genome sequencing (WGS) or whole exome sequencing (WES) of blood samples, but only at participating sites (see Section 4.5.9).

Screening serum, blood, plasma, and PBMC samples, including those collected from patients who do not enroll in the study, may be used for future research and/or development of disease-related tests or tools.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.10), biological samples will be destroyed no later than the time of completion of the final Clinical Study Report (CSR), with the following exceptions:

- Serum samples collected for PK or immunogenicity analysis may be needed for additional immunogenicity characterization and for PK or immunogenicity assay development and validation; therefore, these samples will be destroyed no later than 5 years after the final CSR has been completed.
- Blood, serum, plasma, and PBMC samples collected for autoantibodies, biomarker research, and biomarker assay development will be destroyed no later than 10 years after the final CSR has been completed. However, the storage period will be in accordance with the Institutional Review Board/Ethics Committee (IRB/EC) approved Informed Consent Form and applicable laws (e.g., health authority requirements).

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Data arising from sample analysis, including data on genomic variants, will be subject to the confidentiality standards described in Section 8.4.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Assessment of CRP, fibrinogen, satralizumab pharmacokinetics, IL-6, sIL-6R, ADAs, immunoglobulins, and complement (C3, C4, and CH50) will be performed in a blinded manner and results will not be available to site and Sponsor until database lock for

analysis of the DB period. The iDMC will perform periodic unblinded safety reviews, which will include the laboratory parameters that are blinded to the sponsor and site.

4.5.7 Electrocardiograms

Single ECG recordings will be obtained at specified timepoints, as outlined in the schedule of activities (see Appendix 1 and Appendix 2), and may be obtained at unscheduled timepoints as indicated.

All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws). Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site. The following should be recorded in the appropriate eCRF: heart rate, RR interval, QRS interval, PR duration, uncorrected QT interval, and QT interval corrected through use of Fridericia's formula (QTcF) on the basis of the machine readings of the individual ECG tracings. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF. New or worsened abnormalities should be recorded as adverse events if clinically significant.

If at a particular timepoint the mean QTcF is $>$ 500 ms and/or $>$ 60 ms longer than the baseline value, another ECG must be recorded, ideally within the next 5 minutes, and ECG monitoring should continue until QTcF has stabilized on two successive ECGs. The Medical Monitor should be notified. SOC treatment may be instituted per the discretion of the investigator. If a PK sample is not scheduled for that timepoint, an unscheduled PK sample should be obtained. The investigator should also evaluate the patient for potential concurrent risk factors (e.g., electrolyte abnormalities, co-medications known to prolong the QT interval, severe bradycardia).

4.5.8 Clinical Outcome Assessments

PRO and clinician-reported outcome (ClinRO) instruments will be completed to assess the treatment benefit of satralizumab. In addition, PRO instruments will enable the capture of each patient's direct experience with satralizumab.

PRO data will be collected through use of the following instruments:

- MG-ADL
- MG-QOL 15r
- Quality of Life in Neurological Disorders (Neuro–QoL) Fatigue Subscale

- EuroQoL EQ-5D-5L (EuroQoL 5-Dimension Questionnaire)

ClinRO data will be collected through use of the following instruments:

- QMG
- MGC

Efficacy assessments scheduled on designated visits should be completed pre-dose on each dosing day and should be performed **prior to any other study specific assessment**, except for obtaining informed consent at screening. It is recommended that patients complete the efficacy assessments in the morning. If the clinical efficacy assessments cannot be performed in the morning, they should be performed at the same time of the day throughout the study. Efficacy assessments should be performed **in the following sequence** (at each study visit including these assessments): MG-ADL, MG-QOL 15r, Neuro–QoL Fatigue subscale, EuroQoL EQ-5D-5L, QMG, and MGC. AChEIs must be held for at least 10 hours before the QMG, and MGC assessments (consistent with the revised manual for the QMG test as recommended by the MGFA).

4.5.8.1 Data Collection Methods for Clinical Outcome Assessments

Clinical outcome assessments will be self-administered (MG-QOL 15r, Neuro–QoL Fatigue Subscale, EuroQoL EQ-5D-5L) or interviewer-administered (MG-ADL, QMG, MGC) at specified timepoints during the study (see the schedule of activities in Appendix 1 and Appendix 2). Instruments will be administered before the patient receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of study treatment, unless otherwise specified.

PRO instruments, translated into the local language as appropriate, will be provided by the Sponsor to enable the appropriate instruments to be administered, in the correct order, at each specified timepoint.

During clinic visits, PRO instruments should be administered as outlined below.

- Patients' health status should not be discussed prior to administration of the instruments.
- Sites must administer the official version of each instrument, as provided by the Sponsor. Instruments must not be copied from the protocol.
- Sites should allow sufficient time for patients to complete the instruments, estimated to be 20 minutes.
- Sites should administer the instruments in a quiet area with minimal distractions and disruptions.
- MG-ADL will be administered by an examining investigator.
- Patients should be instructed to answer questions to the best of their ability; there are no right or wrong answers.

- Site staff should not interpret or explain questions, but may read questions verbatim upon request.
- Patients should not obtain advice or help from others (e.g., family members or friends) when completing the instruments.
- Site staff should review all completed instruments and should ask the patient to rectify any response that is not clearly marked in the appropriate location. If a response is missing, site staff should ask the patient to complete the item or confirm that the item was intentionally left blank.

ClinRO instruments will be completed at the clinic by the examining investigator at specified timepoints during the study (see the schedule of activities in Appendix 1 and Appendix 2). ClinRO instruments will be administered **prior to completion of the physical examination**, **prior to any safety assessments, and prior to the administration of study treatment**. The instruments will be provided by the Sponsor. The examining investigator must complete the official version of each ClinRO instrument provided by the Sponsor. Instruments must not be copied from the protocol.

4.5.8.2 Description of Clinical Outcome Assessment Instruments

Myasthenia Gravis Activities of Daily Living (MG-ADL)

This instrument was developed for the trial of IVIg by Wolfe and colleagues (Wolfe et al. 2019). This is a PRO that combines two items on daily life activities—ability to brush teeth or comb hair, and limitations in the ability to rise from a chair—with six items reflecting other MG symptoms: diplopia, ptosis, difficulty chewing, difficulty swallowing, voice/speech problems, and respiratory symptoms. Each item is scored between 0 and 3, and total scores range from 0 to 24, with higher scores indicating more disease severity. The recall period should be the last 7 days prior to MG-ADL assessment. An examining investigator (or designee) will administer the MG-ADL instrument.

A sample of the MG-ADL questionnaire is included in Appendix 6.

Quantitative Myasthenia Gravis (QMG) Score

The QMG score was developed in the context of a clinical trial in MG and originally had eight items (Besinger et al. 1983); it was subsequently modified increasing the number of items to 13 (Tindall et al. 1987). The QMG has several items that measure endurance or fatigability, taking into account the fluctuating nature of the disease. These are as follows: ptosis, diplopia on lateral gaze, eye closure (orbicularis oculi) weakness, swallowing 1/2 cup of water, speech during or following counting aloud from 1 to 50, percent predicted forced vital capacity, grip strength (two items), arm endurance (two items), leg endurance (two items), and neck flexion endurance. All items are scored on a scale from 0 to 3, and total scores range from 0 to 39; higher scores indicate greater disease severity. The test should be performed by the examining investigator as described in the QMG Manual.

A sample of the QMG questionnaire is included in Appendix 7.

Myasthenia Gravis Composite (MGC)

The MGC was developed recently aiming for a simple yet comprehensive measure of MG severity. It was developed by combining items from other MG measures, on the basis of their performance in two clinical trials of mycophenolate in MG (Sanders et al. 2008; Muscle Study Group 2008). The final measure has ten items: two ocular (diplopia and ptosis); four manual muscle test items (facial, neck, shoulder abduction, and hip flexion strength), and four patient-reported items (chewing, swallowing, breathing, and speech). The patient-reported items have to be read to the patients, and the whole scale is completed by the examining investigator. Total scores range from 0 to 50 for which higher scores indicate greater disease severity.

Patients *(adult and adolescent patients randomized in the DB period at study start)* on AChEI should remain on stable doses throughout the DB period and until Week 12 of the OLE. AChEI should not be taken for at least 10 hours prior to QMG and MG composite testing at each visit (except screening visit), in order to reduce fluctuations in performance on functional tests due to the temporary symptomatic effects associated with AChEI use.

A sample of the MGC questionnaire is included in Appendix 8.

Myasthenia Gravis Quality of Life 15 revised version (MG-QOL15r)

The MG-QOL15r was developed by simplifying the MG-QOL60 (Burns TM, Muscle Nerve 2008). The instrument contains 15 items assessing the mobility (nine items), symptoms (three items), and general contentment and emotional well-being (three items). Individual items are scored from 0 to 2 and the resulting measure scores ranges from 0 to 30, and higher scores indicate worse health-related quality of life (HRQoL).

A sample of the MG-QOL15r questionnaire is included in Appendix 9.

Neuro–QoL Fatigue Subscale

The Neuro–QoL is a validated tool designed to evaluate the HRQoL in patients with chronic neurological disease (Gershon et al. 2012). The Fatigue Subscale is implemented as an eight-item, stand-alone short form that assesses the multi-dimensional aspects of fatigue ranging from general tiredness to debilitating exhaustion that Impacts activities of daily living. Raw scores range from 8 to 40 with higher values indicating greater fatigue.

A sample of the Neuro–QoL Fatigue Subscale is included in Appendix 13.

EuroQoL EQ-5D-5L

The EuroQoL EQ-5D-5L is a validated self-report health status questionnaire that is used to calculate a health status utility score for use in health economic analyses (EuroQoL Group 1990; Brooks 1996; Herdman et al. 2011; Janssen et al. 2013) (see Appendix 10). There are two components to the EQ-5D-5L: a five-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and

anxiety/depression, as well as a Visual Analogue Scale (VAS) that measures health state. The EQ-5D-5L is designed to capture the patient's current health status. Published weighting systems allow for creation of a single composite score of the patient's health status. The EQ-5D-5L takes approximately 3 minutes to complete. It will be used in this study for informing pharmacoeconomic evaluations.

A sample of the EQ-5D-5L questionnaire is included in Appendix 10.

Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a tool used to assess the lifetime suicidality of a patient and to track suicidal events throughout treatment. The scale will be administered at the time points indicated in the schedule of activities (see Appendix 1 and Appendix 2) for prompt recollection of suicidal ideation, including the intensity of the ideation, behavior and attempts with actual and potential lethality. The "C-SSRS at baseline" will be collected at baseline, and the "C-SSRS since last visit" will be collected at subsequent visits.

Examples of the C-SSRS forms are included in Appendix 11 and Appendix 12.

4.5.9 Blood Samples for Whole Genome Sequencing or Whole Exome Sequencing

At participating sites, blood samples will be collected for DNA extraction to enable WGS or WES to identify variants that are predictive of response to study drug, are associated with progression to a more severe disease state, are associated with susceptibility to developing adverse events, can lead to improved adverse event monitoring or investigation, or can increase the knowledge and understanding of disease biology and drug safety. Research will be aimed at exploring inherited characteristics. The samples may be sent to one or more laboratories for analysis.

Collection and submission of blood samples for WGS or WES is contingent upon the review and approval of the exploratory research by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for WGS or WES, this section of the protocol (Section 4.5.9) will not be applicable at that site.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events. Data will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Blood samples collected for WGS or WES are to be stored until they are no longer needed or until they are exhausted. However, the storage period will be in accordance with the IRB/EC -approved Informed Consent Form and applicable laws (e.g., health authority requirements).

Refer to Section 4.5.6 for details on use of samples after patient withdrawal, confidentiality standards for data, and availability of data from biomarker analyses.

4.5.10 Optional Samples for Research Biosample Repository

4.5.10.1 Overview of the Research Biosample Repository

The Research Biosample Repository (RBR) is a centrally administered group of facilities used for the long-term storage of human biological specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR samples will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Samples for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR samples will be analyzed to achieve one or more of the following objectives:

- To study the association of biomarkers with efficacy or disease progression
- To identify safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation
- To increase knowledge and understanding of disease biology and drug safety
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.10.2 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.10) will not be applicable at that site.

4.5.10.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes and assay development, including, but not limited to, research on biomarkers related to satralizumab, diseases, or drug safety:

- Leftover blood, serum, plasma, PBMCs, and any derivatives thereof (e.g., DNA, RNA, proteins, peptides)
- Serum and plasma samples collected at baseline and subsequent visits for RBR

The above samples may be sent to one or more laboratories for analysis, which may include proteins, metabolites, and immune cell assessment and/or profiling. DNA samples may be used for the analysis of germline or somatic variants via WGS, WES, or other genomic analysis methods. Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events.

Data generated from RBR samples will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RBR samples are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC approved Informed Consent Form and applicable laws (e.g., health authority requirements).

4.5.10.4 Confidentiality

RBR samples and associated data will be labeled with a unique patient identification number.

Patient medical information associated with RBR samples is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Given the complexity and exploratory nature of the analyses of RBR samples, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Data generated from RBR samples must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR data will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

4.5.10.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RBR. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RBR samples. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the RBR Research Sample Informed Consent eCRF.

In the event of an RBR participant's death or loss of competence, the participant's samples and data will continue to be used as part of the RBR research.

4.5.10.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR samples have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the patient. However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her RBR samples during the study, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. If a patient wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

global.rcr-withdrawal@roche.com

A patient's withdrawal from this study does not, by itself, constitute withdrawal of consent for testing of RBR samples. Likewise, a patient's withdrawal of consent for testing of RBR samples does not constitute withdrawal from this study.

4.5.10.7 Monitoring and Oversight

RBR samples will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of samples as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

Patients must permanently discontinue study treatment if they experience any of the following:

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient
- Pregnancy
- Malignancy
- Severe hypersensitivity or anaphylactic reaction to satralizumab
- GI perforation
- Unacceptable toxicity
- Significant non-compliance with protocol procedures
- Meets the discontinuation criteria in the risk mitigation and dose modification strategy (see Section 5.1)

Patients may need to permanently discontinue study treatment if they receive prohibited therapy.

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced.

It is important to distinguish between "withdrawal from treatment / discontinue treatment" and "withdrawal from study." Patients who withdraw from treatment should be encouraged to remain in the study for the full duration of the SFU.

Patients who discontinue study treatment during the DB period for any reason should continue with all remaining assessments defined in the protocol. However, patients who

are unwilling to return to the clinic for all assessments will be asked to complete an EOT visit within 4 weeks and a SFU visit 12 weeks *after* the final dose of study drug.

Patients who discontinue study treatment during the OLE period will be asked to complete the EOT visit within 4 weeks and *a* SFU visit 12 weeks *after* the final dose of study drug.

4.6.2 Patient Discontinuation from the Study

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time.

Reasons for patient discontinuation from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure
- Adverse event
- The participant enrolls into another interventional clinical study in which an investigational treatment or approved therapy for investigational use is administered.
- Loss to follow-up
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

Every effort should be made to obtain a reason for patient discontinuation from the study. The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced.

4.6.3 Study Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

4.6.4 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence

- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Satralizumab is not approved for the treatment of gMG. The safety plan for patients in this study is based on clinical experience with satralizumab in completed and ongoing studies, and safety risks observed with medicines in the same class (i.e., anti–IL-6R antibodies). The anticipated important safety risks for satralizumab are outlined below. Please refer to the most recent Satralizumab Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at higher risk for toxicities (see Section 4.1.2). Patients will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events, including criteria for treatment interruption or discontinuation, are provided below.

5.1.1 Risks Associated with Satralizumab

5.1.1.1 Infections

Treatment with IL-6R inhibitors may increase the risk of infections, including serious infections. Treatment with IL-6R inhibitors suppresses acute-phase reactions (fever, increase in CRP, etc.) induced by IL-6 and accordingly suppresses signs and symptoms associated with infection, which may delay the detection of infection.

Reactivation of chronic hepatitis B has been observed with other treatments that affect the immune system. TB reactivation has also been reported with other anti–IL-6R antibodies.

The allowed IST background treatments (OCSs, azathioprine, mycophenolate mofetil, cyclosporin A, tacrolimus) for patients with gMG participating in this study have been associated with serious infections.

The following participants will be excluded from this study (see Section 4.1.2):

- Participants with active or recurrent bacterial, viral, fungal, mycobacterial infection, or other infection (excluding fungal infection of nail beds or dental caries) at baseline
- Participants with infection requiring hospitalization or treatment with IV anti--infective agents within 4 weeks prior to baseline visit or oral anti-infective agents within 2 weeks prior to baseline visit

- Participants with evidence of latent or active tuberculosis (excluding patients receiving chemoprophylaxis for latent TB infection)
- Participants with positive screening tests for hepatitis B or hepatitis C
- Participants who received any live or live attenuated vaccine within 6 weeks prior to baseline

Management of Infections and Serious Infections

- Patients should be closely monitored for the development of signs and symptoms of infection, because signs and symptoms of acute inflammation may be lessened as a result of suppression of the acute phase reactants.
- Patients must be instructed to contact their physician immediately when any symptoms suggesting infection appear, in order to ensure rapid evaluation and appropriate treatment.
- If a patient develops an infection, administration of the study drug is to be interrupted until the infection is controlled.
- If a patient develops a serious infection or Grade ≥3 infection, administration of the study drug is to be interrupted until the infection is resolved. Upon resolution of the infection, the treating physician should conduct a benefit–risk assessment before resuming treatment with the study drug.
- If a participant develops hepatitis B infection (new onset or reactivation), the study drug should be discontinued.
- Live or live attenuated vaccines are not to be given during the course of the study and within 6 weeks prior to baseline as clinical safety has not been established.

Treatment of Infections and Serious Infections

Treatment with the following antibiotics should be avoided if possible, because they have been associated with exacerbations of MG (see Section 4.4.2 for cautionary therapy):

- Macrolide antibiotics (e.g., erythromycin, azithromycin, clarithromycin)
- Aminoglycoside antibiotics (e.g., gentamycin, neomycin, tobramycin)
- Treatment with antibiotics telithromycin and fluoroquinolones (e.g., ciprofloxacin, moxifloxacin and levofloxacin) is prohibited during the study (see Section 4.4.3 for Prohibited Therapy)

5.1.1.2 Hypersensitivity

Anaphylaxis and hypersensitivity reactions are considered a potential risk for all biologic medications, including satralizumab.

The symptoms or signs of hypersensitivity include, but are not limited to, blood pressure decrease, dyspnea, loss of consciousness, dizziness, nausea, vomiting, fever, chills, urticaria, itchiness, flushing, etc.

Management of Possible Hypersensitivity Reactions to Satralizumab

- SC injections should be administered at the study sites. Patients should stay in the clinic/hospital for at least one hour after study drug administration for the first five doses of study drug in order to receive treatment immediately in case anaphylaxis occurs. Study sites should have medications (e.g., corticosteroid, antihistamine, and epinephrine) and access to resuscitation facilities.
- Administration of the study drug outside of the study site might be allowed during the OLE period, from OLE Week 24 onward (see Section 4.3.2), if the investigator determines that it is appropriate.
- Patients and caregivers will be provided with emergency contact information by the site. Patients and caregivers should be instructed to recognize the signs and symptoms of hypersensitivity reactions and to seek immediate medical attention if the patient develops symptoms of acute hypersensitivity reactions. Patients and caregivers should confirm with the investigator whether treatment with study drug may be continued.
- If an anaphylactic reaction or other serious hypersensitivity reaction occurs, the study drug should be discontinued.
- For other hypersensitivity reactions, a decision to continue or discontinue treatment with satralizumab will be made by the investigator in consultation with the Medical Monitor, taking into account the benefits and risks.

5.1.1.3 Liver Enzyme and Bilirubin Elevations

It has been reported that IL-6 appears to have a hepato-protective effect on various forms of liver injury and promotes hepatocyte regeneration.

During the DB period of the Phase III studies in NMOSD patients, mild and moderate elevations of liver transaminases (ALT or AST) were observed with satralizumab treatment. Elevations of ALT or AST $> 3 \times$ ULN were not associated with increases in bilirubin.

Patients with AST or ALT $> 1.5 \times$ ULN at screening, will be excluded from the study.

Liver function markers should be closely monitored, especially when satralizumab is administered concomitantly with hepatotoxic drugs, or to patients with elevated transaminases (in the range of ULN to $1.5 \times$ ULN). Some of the allowed background therapies, mycophenolate mofetil, azathioprine, tacrolimus, and cyclosporine A, are hepatotoxic. Please refer to the local prescribing information of the background treatment(s) for details on their individual safety profile(s).

Recommended dose interruption or discontinuation for elevated liver enzymes is shown in Table 8.

Table 8 Management of Patients with Elevated Transaminases (ALT and/or AST)

ALT or AST Values	Action to Be Taken
>1 to $3\times$ ULN	• Reduction (interruption if necessary) of concomitant hepatotoxic drugs could be considered. • For persistent increases in this range, the study drug could be interrupted until AST and ALT is below ULN.
>3 to $5\times$ ULN	• Don't dose study drug, and laboratory tests (ALT, AST, ALP and TBL) should be repeated within 72 hours to confirm value. Patients who are far away from the trial site may be retested locally if prompt return to the trial site is difficult. • The presence of clinical symptoms should be queried. • Study drug should be interrupted until AST and ALT is below $3\times$ ULN. Follow recommendations outlined above for ALT/AST values >1 to $3\times$ ULN. • If at least one of following is associated with the ALT/AST increase, study drug should be discontinued immediately: – TBL $>2\times$ ULN and/or – INR $>1.5\times$ ULN and/or – Appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia
$>5\times$ ULN	• Don't dose study drug. Laboratory tests (ALT, AST, ALP, and TBL) should be repeated within 72 hours. If value is confirmed, study drug should be discontinued immediately and gastroenterologist should be contacted. • The presence of clinical symptoms should be queried. • If prompt return to the trial site is difficult, the patients may be retested locally. • Repeat LFT weekly until AST or ALT are $\leq 1.5\times$ ULN.

LFT= liver function test; TBL=total bilirubin; ULN=upper limit of normal.

5.1.1.4 Neutropenia

In the DB period of the Phase III studies in NMOSD patients, decreases in neutrophil counts (including Grade 3 and Grade 4) occurred following treatment with satralizumab. The majority of neutrophil decreases were transient or intermittent.

Participants with a low neutrophil count ($<2\times 10^3/\mu L$) will be excluded from the study (see Section 4.1.2.4).

Recommended dose interruption or discontinuation for absolute neutrophil counts (ANC) decreases are shown in Table 9.

Table 9 Management of Neutropenia Low Neutrophil Count

ANC (/μL)	Action to Be Taken
>1,000	• Maintain dose.
500–1,000	• If neutropenia persists, the study drug should be interrupted until ANC is above 1,000/μL (for restarting study drug administration please refer to Section 4.3.2.2). • If ANC was under 1,000/μL at the previous laboratory test, ANC must be checked before treatment with the study drug (e.g., ANC test at site).
<500	• Study drug should be discontinued.

ANC = absolute neutrophil count.

5.1.1.5 Thrombocytopenia

In Phase III studies in NMOSD patients, decreases in platelet counts were observed in patients treated with satralizumab. The majority of the decreased platelets were transient and not below 75×10^9/L.

Patients with Platelet count $< 10 \times 10^4$/μL at screening will be excluded from the study (see Section 4.1.2.4).

Recommended dose interruption on the basis of platelet counts are shown in Table 10.

Table 10 Management of Low Platelet Count

Platelet Count (/μL)	Action
>75,000	• Maintain dose.
50,000–75,000	• If thrombocytopenia persists, the study drug should be interrupted until platelet count is above 75,000 cells/μL (for restarting study drug administration please refer to Section 4.3.2.2).
<50,000	• The study drug should be discontinued.

5.1.1.6 Elevations in Lipid Levels

In DB period of the Phase III studies in NMOSD patients, elevations in total cholesterol and triglycerides were observed more often in patients treated with satralizumab compared with placebo.

Elevations in lipid levels in study participants should be managed according to local guidelines.

5.1.1.7 Laboratory Abnormalities Associated with the Pharmacodynamic Effect of Satralizumab

In addition to the above abnormal laboratory parameters, in the Phase III studies with satralizumab in NMOSD patients, decreases in CRP, fibrinogen and complement (C3, C4 and CH50) were observed, which are anticipated PD effects of satralizumab.

5.1.1.8 CYP450 Enzyme Normalization

Elevation of serum IL-6 levels is known to be associated with inhibition of CYP450 enzyme activity. Blockade of IL-6 signaling by satralizumab may result in normalization of CYP450 activity and therefore increases in the metabolism of CYP450 substrates. Caution should therefore be exercised when starting or discontinuing study treatment in patients also receiving substrates of CYP450 3A4, 1A2, 2C9 or 2C19, including some immunosuppressive agents (e.g., tacrolimus, cyclosporine), and particularly those with a narrow therapeutic index (such as warfarin, carbamazepine, phenytoin, and theophylline), and doses adjusted if needed.

Please refer to Section 4.4.2.1 for further details.

Given the prolonged terminal drug-elimination half-life of satralizumab, the effect of satralizumab may persist for several months after stopping therapy.

5.1.2 Other Risks Associated with Drugs in the Same Class

5.1.2.1 Gastrointestinal Perforations (Complications of Diverticulitis)

GI perforations have been reported rarely in patients with RA treated with other anti–IL-6R antibodies. IL-6R inhibition may suppress the acute symptoms (abdominal pain, pyrexia, etc.) associated with diverticulitis, etc., causing delayed diagnosis and progression to perforation.

Patients with a history of diverticulitis or concurrent severe GI disorders (such as symptomatic diverticulosis) that, in the investigator's opinion, may lead to increased risk of complications such as GI perforation are excluded from the study.

Special caution should be exercised in those patients who receive background therapy that has been associated with a risk of GI perforation, including tacrolimus, azathioprine, mycophenolate mofetil, and OCSs. Please refer to the local prescribing information of the background therapy for additional details on the risk of GI perforation.

Management of Patients with (Suspected) Gastrointestinal Perforation

- Patients presenting with symptoms potentially indicative of complicated diverticulitis, such as abdominal pain, hemorrhaging, and/or unexplained change in bowel habits with fever should be evaluated promptly for early identification of diverticulitis which can be associated with GI perforation and appropriate measures taken. The study drug should be discontinued for patients who develop GI perforation. Patients should be made aware of the symptomatology potentially indicative of complicated

diverticular disease, and they should be instructed to alert their healthcare provider as soon as possible if these symptoms arise.

- In patients who receive OCS and/or non-steroidal anti-inflammatory drugs, prophylactic treatment with proton pump inhibitors or H2 blocker should be considered.

5.1.2.2 Malignancies

Although malignancies have been reported in patients given other IL-6R antibodies, there have been no reports to date that there is an appreciable increase in the occurrence of malignancies. No increased risk of malignancies has been observed in clinical trials with satralizumab.

Patients with a history of malignancy within the last 5 years prior to study entry, including solid tumors, hematologic malignancies and in situ carcinoma (except basal cell and squamous cell carcinomas of the skin, or in situ carcinoma of the cervix uteri that have been completely excised and cured), will be excluded from the study (see Section 4.1.2.3).

Management of Patients with Malignancies

The study drug should be discontinued in patients with malignancies (with the exception of local basal or squamous cell carcinoma of the skin that is completely excised with free margins).

5.1.2.3 Demyelinating Disorders

Demyelinating diseases, including multiple sclerosis and chronic inflammatory demyelinating polyneuropathy, have been reported in patients with RA administered with another anti–IL-6R antibody, but it is not known whether there is a causal relationship. If symptoms suggestive of a demyelinating disorder are reported, a complete neurological examination should be performed and additional diagnostic studies performed if indicated.

5.1.3 Concomitant Immunosuppressive Treatment

Patients receiving background treatment with allowed ISTs should also be informed of the risks associated with taking OCSs, azathioprine, mycophenolate mofetil, tacrolimus, and cyclosporine A, as per local prescribing information.

5.1.4 Management of Patients Who Experience Adverse Events

5.1.4.1 Treatment Interruption or Discontinuation

Satralizumab treatment may be interrupted or discontinued in patients who experience an adverse event or abnormal laboratory value (see Section 5.1.1). Satralizumab may be suspended for reasons other than adverse events (e.g., surgical procedures) *at the investigator's discretion following consultation with the Medical Monitor*. The investigator *may consult* the Medical Monitor *to* determine the acceptable length of treatment interruption.

5.1.4.2 Management Guidelines for Adverse Events

Guidelines for management of specific adverse events are presented in Section 5.1.1.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Sections 5.3.5.9 and 5.3.5.10 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.11)

- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE]; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study drug, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

5.2.4 Selected Adverse Events

Additional data will be collected and/or analyzed for the following selected adverse events:

- Infections
- Injection reactions, adverse events considered injection reactions, which occur during or within 24 hours after study drug administration and are judged to be related to the study drug injection

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6.
The investigator is also responsible for reporting medical device complaints (see Section 5.4.4).

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact.
All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events will be reported until 12 weeks after the final dose of study drug.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. Table 11 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 11 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b, c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event

- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Injection Reactions

Adverse events, considered to be injection reactions, that occur during or within 24 hours after study drug administration and are judged to be related to study drug injection should be captured as a diagnosis (e.g., "injection related reaction", "injection-site reaction" or "anaphylactic reaction") on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Injection Reaction eCRF. If a patient experiences both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Injection Reaction eCRF.

5.3.5.2 Diagnosis versus Signs and Symptoms

For adverse events other than injection reactions (see Section 5.3.5.1), a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.

- If a severe GI hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.5 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ ULN) in combination with either an elevated total bilirubin ($>2\times$ ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ ULN in combination with total bilirubin $>2\times$ ULN
- Treatment-emergent ALT or AST $>3\times$ ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.8 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). This includes death attributed to progression of gMG.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

If the death is attributed solely to progression of gMG, "generalized myasthenia gravis progression" should be recorded on the Adverse Event eCRF.

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.9 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.10 Lack of Efficacy or Worsening of Generalized Myasthenia Gravis

Events that are clearly consistent with the expected pattern of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. If there is any uncertainty as to whether an event is due to clinical deterioration (gMG exacerbation), it should be reported as an adverse event.

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study drug administration)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
  - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease
  - The patient has not experienced an adverse event
- Hospitalization due solely to progression of the underlying disease, gMG

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.5.12 Cases of Overdose, Medication Error, Drug Abuse, or Drug Misuse

Overdose (accidental or intentional), medication error, drug abuse, and drug misuse (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Intentional overdose: intentional administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.
- Drug abuse: intentional excessive use of a drug that may lead to addiction or dependence, physical harm, and/or psychological harm
- Drug misuse: intentional deviation in the administration of a drug that does not qualify as drug abuse

  In cases where drug is to be self-administered by the patient, drug misuse could involve the drug being administered to someone other than the patient.

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria *or qualifies as an adverse event of special interest*, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). For satralizumab or matching placebo, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the adverse event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Drug abuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug misuse" boxes.

In addition, all special situations associated with satralizumab or matching placebo, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.

- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.
- Drug abuse that does not qualify as an overdose: Enter the drug name and "drug abuse" as the event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the drug name and "drug misuse" as the event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug misuse" boxes.
- Drug administered to someone other than the patient: Enter the drug name and "patient supplied drug to third party" as the event term. Check the "Drug misuse" box.

As an example, an accidental overdose that resulted in a headache would require two entries on the Adverse Event eCRF, one entry to report the accidental overdose and one entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

5.3.5.13 Patient-Reported or Clinician-Reported Outcome Data

Adverse event reports will not be derived from PRO or ClinRO data by the Sponsor. Sites are not expected to review the PRO or ClinRO data for adverse events.

5.3.5.14 Safety Biomarker Data

Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on patient management.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)

- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)
- Medical device complaints (see Section 5.4.4 for details on reporting requirements)

For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Medical Monitors and Emergency Medical Contacts

Contact Information for All Sites

To ensure the safety of study patients access to Medical Monitor is available 24 hours per day, 7 days per week. An Emergency Medical Call Center will also be available 24 hours per day, 7 days per week. The Emergency Medical Call Center will connect the investigator with an Emergency Medical Contact, provide medical translation service if necessary, and track all calls. Contact information, including toll-free numbers for the Emergency Medical Call Center, will be distributed to investigators.

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The paper *Clinical Trial Adverse Event/Special Situations Form* provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 12 weeks after the final dose of study drug. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the

electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper *Clinical Trial Adverse Event/Special Situations Form* provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur > 12 weeks after the final dose of study treatment are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed *through the Informed Consent Form* to immediately inform the investigator if they become pregnant during the study or within 3 months after the final dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Nonclinical studies with satralizumab did not indicate harmful effects with respect to reproductive toxicity. The follow up of partner pregnancies is therefore not required in this study. Please refer to the Satralizumab Investigator's Brochure for additional information on reproductive toxicity.

5.4.3.3 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4.4 Reporting Requirements for Medical Device Complaints

In this study, PFS with NSD/EFF is considered a medical device constituent part of the integral medicinal product. The investigator must report all medical device related complaints to the Sponsor. The investigator should document as much information as possible on the IMP Deviation Form, including the product batch number, and forward the form to the Sponsor immediately (i.e., no more than 24 hours after learning of the event) (refer to the pharmacy manual for further details). If the medical device constituent parts result in an adverse event to the study patient, the event must be reported on the Adverse Event eCRF and submitted through the EDC system. If the event is serious, the Adverse Event eCRF must be completed immediately (i.e., no more than 24 hours after learning of the event), as outlined in Section 5.4.2.

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 12 weeks after the final dose of study drug), if the event is believed to be related to prior study drug treatment. These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper *Clinical Trial Adverse Event/Special Situations Form* using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

The Sponsor has a legal responsibility to notify regulatory authorities about the safety of a study treatment under clinical investigation. The Sponsor will comply with regulatory requirements for expedited safety reporting to regulatory authority (which includes the use of applicable systems, such as EudraVigilance), IRBs, ECs, and investigators.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events through use of the reference safety information in the document listed below:

Drug	Document
Satralizumab	Satralizumab Investigator's Brochure

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

Full details of all statistical issues and planned statistical analyses will be specified in a separate SAP, which will be finalized prior to the locking and unblinding of the study database.

This study will compare 120 mg or 180 mg satralizumab (for patients with body weight ≤ 100 kg or > 100 kg respectively) with placebo, administered for 24 weeks, in patients with gMG as defined by the study inclusion and exclusion criteria. Patients will be required to be on stable background therapy at baseline and during the DB treatment period, as outlined in Section 3.1.

Statistical analysis will follow the estimand framework and considers three intercurrent events:

- Withdrawal from study treatment
- Receiving a rescue therapy
- Treatment interruption due to infection

The primary comparison of interest is the difference between the placebo and satralizumab groups in the change from baseline to Week 24 in the total MG-ADL score *on* the *AChR+ population*, irrespective of treatment adherence or use of rescue medication.

Analysis of primary and secondary endpoint will be conducted on the mITT population unless otherwise specified. The mITT population consists of all patients who have a baseline and at least one post-baseline DB period MG-ADL assessment. Adolescent patients enrolled after the last adult randomized will not be part of the mITT population. For additional subgroup analysis, subgroups within the mITT population will be considered.

6.1 DETERMINATION OF SAMPLE SIZE

Determination of sample size is based on all globally *AChR+* enrolled patients. In this study, approximately *160 AChR+ patients and up to 25 AChR – (MuSK + or LRP4 +)* patients will be enrolled. *Participants enrolled in the DB period will be* randomized in a 1:1 ratio to each treatment group (satralizumab or placebo). Randomization will be stratified by baseline SOC treatment, region, and autoantibody type as described in Section 3.1. *Adolescent patients will be enrolled directly in the OLE period and will receive open-label satralizumab treatment (see Section 3.1.3).*

The estimated sample size required to demonstrate efficacy with regard to the MG-ADL is based on the AChR+ population and the following assumptions:

- The primary hypotheses test in the AChR+ population is the difference between the placebo and satralizumab groups in the change from baseline to Week 24 in total MG-ADL score.
- The assumed change from baseline to Week 24 in the placebo group is 2.3 points.
- The assumed change from baseline to Week 24 in the satralizumab group is 4.3 points.
- The assumed change from baseline accounts for approximately 10% of patients in the satralizumab group and approximately 20% of patients in the placebo group receiving rescue therapy.
- The SD of the change from baseline to Week 24 is 3.97 in both the placebo and satralizumab groups.
- The assumed study treatment withdrawal rate is 10%.

The assumptions are based on data reported in Howard et al. (2017).

Based on these assumptions and using a two-sided α level of 0.05, the sample size to achieve 85% power was estimated at 160 patients (80 per group) in the AChR+ population. Under the assumption that up to 25 patients meeting the study eligibility criteria will be AChR−(MuSK+ or LRP4+), the total study sample size will be approximately 185 patients. This sample size also provides approximately 80% power for an analysis of the difference between the placebo and satralizumab groups in the proportion of MG-ADL responders in the mITT and AChR+ population. This power calculation assumes a 50% response rate in the placebo group and a 75% response rate in the satralizumab group.

Following the PK interim analysis, the iDMC recommended that the initial doses (120 mg ≤100 kg >180 mg) should be retained, therefore patients (from both placebo and satralizumab groups) dosed prior to the dose confirmation will be included in the primary analysis and no patient replacement is required.

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients who enroll, discontinue, or complete the study will be summarized. The frequency and timing of intercurrent events will be summarized including reasons for premature study and study treatment discontinuation, and patients receiving rescue therapy. Enrollment and major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic and baseline characteristics (including age, sex, race, region, MGFA classification, antibody type and background medication use) will be summarized using

means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Summaries will be presented overall and by treatment group.

6.4 EFFICACY ANALYSES

There are two analysis populations for the efficacy analyses:

- All randomized AChR+ patients, with patients grouped according to their randomized treatment
- All randomized patients (OP), with patients grouped according to their randomized treatment

Each efficacy analysis will be conducted on all randomized patients that have at least one postbaseline MG-ADL assessment (mITT population).

6.4.1 Primary Efficacy Estimand

The primary comparison of interest is the difference between the placebo and satralizumab groups in the change from baseline to Week 24 in the total MG-ADL score in the AChR+ population.

If a patient withdraws from treatment, the reason for withdrawal will be classified as either study drug or condition related (SDCR) or not study drug or condition related (NSDCR). More details of this classification will be given in the SAP. The primary comparison will include both patients who withdraw due to SDCR and NSDCR reasons, with the assumption that patients who withdrew due to NSDCR reasons would have continued receiving their randomized treatment.

The primary comparison will be made regardless of whether a patient receives rescue therapy or has a treatment interruption due to infection.

The elements of the primary estimand are defined below. The primary analysis approach and determination of sample size is aligned with the primary estimand.

Population:

- Patients with AChR+ gMG as defined by the study inclusion and exclusion criteria *and who are part of the mITT population*.

Primary efficacy variable: MG-ADL total score

Treatment: satralizumab 120 mg (for patients with body weight ≤ 100 kg) or 180 mg (for patients with body weight > 100 kg) versus matching placebo, administered for 24 weeks, in combination with stable background therapy

Intercurrent events:

- SDCR withdrawal from study treatment: treatment policy

- NSDCR withdrawal from study treatment: hypothetical
- Taking rescue therapy: treatment policy
- Treatment interruption due to infection: treatment policy

Summary measure: The difference in the change from baseline to Week 24 in MG-ADL total score

Supplementary estimands will be detailed in the SAP and will include using a hypothetical approach for the intercurrent event of taking rescue therapy and discrimination between the different types of rescue therapy.

6.4.2 Primary Efficacy Estimator

The primary efficacy analyses will compare satralizumab with placebo at Week 24 in the AChR+ population.

The following null and alternative hypotheses will be tested at a two-sided significance level:

$$H_0: \mu_{satralizumab} = \mu_{placebo} \text{ versus } H_1: \mu_{satralizumab} \neq \mu_{placebo}$$

for which $\mu_{satralizumab}$ and $\mu_{placebo}$ refer to the mean change from baseline to Week 24 in the total MG-ADL score in the satralizumab and placebo groups respectively. The primary efficacy objective is to evaluate the efficacy of satralizumab versus placebo on daily function. Patients will be grouped according to the treatment assigned at randomization.

An estimate of the treatment effect will be computed using a “Mixed Model Repeated Measures” analysis adjusting for the randomization stratification factors (background therapy, autoantibody type, and region) and baseline MG-ADL score.

For NSDCR withdrawals, data will be censored at the time of the treatment withdrawal. Any data collected after NSDCR withdrawal will be disregarded. Missing data following a withdrawal that is determined to be NSDCR will be imputed using multiple imputation with a “Missing at Random” assumption.

Missing data following a withdrawal that is determined to be SDCR will be imputed using reference based multiple imputation with a "Copy Reference" assumption. This approach will only be used if observed data following a treatment withdrawal are not available. Where observed data are available, they will continue to be included in the analysis.

Data following rescue therapy and treatment interruption due to infection will be included in the analysis. Approaches to handle item level missing data will be described in the SAP.

The robustness of the primary estimation method will be explored by a series of sensitivity estimators based on varying assumptions underlying the multiple imputation strategy and classification of treatment withdrawal intercurrent events as SDCR or NSDCR. Additional details will be provided in the SAP.

Patients who discontinue from the study treatment for any reason should continue with all remaining assessments defined during the DB period of the protocol. However, patients who are unwilling to return to the clinic for all assessments will be asked to complete the EOT within 4 weeks and *a* SFU visit 12 weeks *after* the final dose of study drug.

6.4.3 Type I Error Control

The primary and secondary endpoints will be tested using a hierarchical gatekeeping procedure. Where the hierarchical gatekeeping procedure is used, if any test result is not statistically significant, formal testing of subsequent endpoints will not occur. If the primary endpoint is statistically significant, the confirmatory secondary endpoints are tested in the following order:

1. Mean change from baseline in QMG score in AChR+ patients at Week 24
2. Mean change from baseline in MG-QOL 15r total score in AChR+ patients at Week 24
3. Mean change from baseline in MGC total score in AChR+ patients at Week 24
4. Mean change from baseline in MG-ADL score in the overall population (OP) at Week 24
5. Mean change from baseline in QMG score in the OP at Week 24
6. Proportion of AChR+ patients receiving rescue therapy between baseline and Week 24
7. *Mean change from baseline in MG-ADL score in MuSK and LRP4 patients at Week 24*
8. Mean change from baseline in Neuro–QoL Fatigue Subscale total score in AChR+ patients at Week 24

6.4.4 Secondary Efficacy Endpoints

The following secondary efficacy endpoints will be analyzed in the same way as the primary efficacy endpoint, using the primary estimand:

- Mean change from baseline in MG-ADL score in the OP at Week 24
- Mean change from baseline in QMG score (in AChR+ patients and the OP) at Week 24
- Mean change from baseline in MG-QOL 15r total score (in AChR+ patients and the OP) at Week 24
- Mean change from baseline in MGC total score (in AChR+ patients and the OP) at Week 24

- Mean change from baseline in Neuro–QoL Fatigue Subscale total score (in AChR+ patients and the OP) at Week 24

The following secondary efficacy endpoints will be analyzed using the responder estimand and estimator (Section 6.4.5):

- Percentage of AChR+ patients (and patients in the OP) with a ≥ 2-point reduction from baseline in total MG-ADL score at Week 24
- Percentage of AChR+ patients (and patients in the OP) with a ≥ 3-point reduction from baseline in QMG score at Week 24
- Percentage of AChR+ patients (and patients in the OP) with a ≥ 3-point reduction from baseline in total MGC score at Week 24
- Proportion of patients who have achieved minimal disease manifestation (total MG-ADL score of 0 or 1) at Week 24

The following secondary efficacy endpoints will be analyzed using the count estimand and estimator (Section 6.4.6):

- Annualized rate of gMG related exacerbations

The following secondary efficacy endpoints will be analyzed using the duration estimand and estimator (Section 6.4.7):

- Duration (average number of consecutive months that patients show a meaningful improvement, defined as ≥ 2 point reduction from baseline in total MG-ADL score

In addition, the following secondary endpoints will not be analyzed using the estimand framework:

- Proportion of patients with at least one gMG-related exacerbation between baseline and Week 24
- Proportion of patients receiving rescue therapy between baseline and Week 24

6.4.5 Responder Estimand and Estimator

The elements of the responder estimand are defined below using the following endpoint as an example:

- Percentage of AChR+ patients with a ≥ 2-point reduction from baseline in total MG-ADL score at Week 24

The intercurrent event of starting a rescue therapy is handled using a composite strategy and is consequently included in the variable definition below.

Population: Patients with AChR+ gMG as defined by the study inclusion and exclusion criteria.

Secondary efficacy variable: a ≥ 2-point reduction from baseline in total MG-ADL score at Week 24 without rescue therapy

Treatment: satralizumab 120 mg (for patients with body weight ≤ 100 kg) or 180 mg (for patients with body weight > 100 kg) versus matching placebo, administered for 24 weeks, in combination with stable background therapy

Intercurrent events:

- SDCR withdrawal from study treatment: treatment policy
- NSDCR withdrawal from study treatment: hypothetical
- Taking rescue therapy: composite (included in variable definition)
- Treatment interruption due to infection: treatment policy

Summary measure: The difference in the proportion of responders at Week 24

An estimate of the treatment effect will be computed using a Cochran-Mantel-Haenszel test adjusting for the randomization stratification factors (background therapy, autoantibody type, and region). Data following a NSDCR withdrawal from study treatment and any missing data will be imputed using multiple imputation as in the primary estimand.

Two endpoints require different considerations:

- The proportion of patients with at least one gMG related exacerbation
- The proportion of patients receiving rescue therapy between baseline and Week 24

In the first case, it is not possible to start a rescue therapy before observing a gMG related exacerbation. In the second, the event of interest is starting a rescue therapy. Therefore, starting a rescue therapy is not considered an intercurrent event for these endpoints and consequently is not included in the estimand definition.

Supplementary estimands will be detailed in the SAP and will include using a composite approach for the intercurrent event of SDCR withdrawal from study treatment.

6.4.6 Count Estimand and Estimator

The elements of the count estimand are defined below using the AChR+ population as an example:

- Population: Patients with AChR+ gMG as defined by the study inclusion and exclusion criteria
- Secondary efficacy variable: Annualized rate of gMG-related exacerbations defined as the total number of gMG-related exacerbations divided by the patient years at risk
- Treatment: satralizumab 120 mg (for patients with body weight ≤ 100kg) or 180 mg (for patients with body weight > 100kg) versus matching placebo, administered for 24 weeks, in combination with stable background therapy

Intercurrent events:

- SDCR withdrawal from study treatment: treatment policy
- NSDCR withdrawal from study treatment: hypothetical
- Taking rescue therapy: treatment policy
- Treatment interruption due to infection: treatment policy

Summary measure: The ratio of the annualized rates of gMG-related exacerbations at Week 24

An estimate of the treatment effect will be computed using a negative binomial regression model adjusting for the randomization stratification factors (background therapy, autoantibody type, and region).

6.4.7 Duration Estimand and Estimator

The elements of the duration estimand are defined below using the AChR+ population as an example:

- Population: Patients with AChR+ gMG as defined by the study inclusion and exclusion criteria
- Secondary efficacy variable: Number of consecutive visits when a patient achieved a $\geq$ 2-point reduction from baseline in MG-ADL, without receiving rescue therapy
- Treatment: satralizumab 120 mg (for patients with body weight $\leq$ 100 kg) or 180 mg (for patients with body weight $>$ 100 kg) versus matching placebo, administered for 24 weeks, in combination with stable background therapy

Intercurrent events:

- SDCR withdrawal from study treatment: treatment policy
- NSDCR withdrawal from study treatment: hypothetical
- Taking rescue therapy: composite (included in variable definition)
- Treatment interruption due to infection: treatment policy

Summary measure: The difference in the mean duration of meaningful improvement at Week 24

An estimate of the treatment effect will be computed using an ANCOVA adjusting for the randomization stratification factors (background therapy, autoantibody type, and region).

6.4.8 Exploratory Efficacy Endpoints

More details on the definition and analysis of exploratory efficacy endpoints will be given in the SAP.

In addition to the exploratory efficacy endpoint specified in Table 1, subgroup analyses will also be performed in the following sub-groups:

- Patients receiving AChEI monotherapy and/or an OCS as background SOC treatment
- Patients receiving a steroid-sparing IST monotherapy or a combination of a steroid-sparing IST with other treatments (an AChEI and/or an OCS) as background SOC treatment
- MuSK+ patients
- LRP4+ patients
- AChR antibody-seronegative patients
- MGFA Class II patients
- MGFA Class III patients
- MGFA Class IV patients
- *Efficacy endpoints of adolescent patients (aged ≥12 – <18 years old at the time of consent) exposed to satralizumab in the DB or OLE period will be summarized descriptively, without statistical testing and without the estimand framework.*

6.5 SAFETY ANALYSES

The safety analysis population will consist of all *enrolled* patients who received at least one dose of study drug, with patients grouped according to treatment received.

Safety will be assessed through summaries of exposure to study treatment, adverse events, changes in targeted laboratory test results, and changes in vital signs and ECGs.

Study treatment exposure (such as treatment duration, total dose received, and number of cycles and dose modifications) will be summarized with descriptive statistics.

In addition, safety analyses will also be performed in the sub-groups detailed in Section 6.4.8.

6.6 PHARMACOKINETIC ANALYSES

The PK analysis population consists of all patients in the safety analysis set with at least one valid post-dose concentration result with a dosing record and sampling time. The trial will evaluate the PK characteristics of satralizumab treatment over 24 weeks by summary statistics and non-linear mixed effects analysis (population PK). PK samples will also be taken during the OLE study period, to further characterize the PK of satralizumab in gMG over longer term treatment.

The serum concentration at each sampling timepoint will be described with means and standard deviation of C_{trough} irrespective of whether patients receive rescue therapy,

change in baseline therapy for MG, miss a dose, or if study drug administration is delayed, or if they withdraw from treatment before data collection at Week 24. Individual and mean serum-concentration-versus-time curves will be plotted.

Non-linear mixed effects analysis will be performed to analyze the satralizumab concentration–time data collected in the trial. The model to be used was previously developed on the basis of PK data from adult HV and adult and adolescent patients with NMOSD. Further model development may be undertaken if needed in order to achieve a satisfactory description of the data, and the data from this study may be pooled with data from other studies with satralizumab. Population and individual PK and exposure parameters will be generated based on the model. Covariate analysis, including demographic factors and ADA status, will also be performed. Both the satralizumab concentration data and the results of the pop PK analysis will be reported separately from the CSR.

Further details are described in a separate Data Analysis Plan.

6.7 IMMUNOGENICITY ANALYSES

The immunogenicity analysis population will consist of all patients with at least one ADA assessment. Patients will be grouped according to treatment received or, if no treatment is received prior to study discontinuation, according to treatment assigned.

The numbers and proportions of ADA-positive patients and ADA-negative patients at baseline (baseline prevalence) and after drug administration (post-baseline incidence) will be summarized by treatment group. When determining post-baseline incidence, patients are considered to be ADA positive if they show treatment-induced ADA response or treatment-enhanced ADA response. Patients who are ADA-negative or have missing data at baseline, but develop an ADA response following study drug exposure have a treatment-induced ADA response. Patients who are ADA positive at baseline and the titer of one or more post-baseline samples is at least at least 4-fold (0.60 titer unit) greater than the titer of the baseline sample have a treatment-enhanced ADA response. Patients are considered to be ADA-negative if they are ADA-negative or have missing data at baseline and all post-baseline samples are negative, or if they are ADA positive at baseline but do not have any post-baseline samples with a titer that is at least 4-fold (0.60 titer unit) greater than the titer of the baseline sample (treatment unaffected).

The percentage of patients who have positive or negative ADA results for satralizumab will be tabulated. PK, PD, efficacy parameters, and safety will be summarized by anti-satralizumab antibody (i.e., satralizumab ADA) status.

In addition, immunogenicity analyses will also be performed in the sub-groups detailed in Section 6.4.8.

6.8 PHARMACODYNAMIC ANALYSES

Serum IL-6 and sIL-6R levels will be summarized by treatment group and timepoint graphically and descriptively, as appropriate.

6.9 EXPLORATORY BIOMARKER ANALYSES

Exploratory biomarkers will be summarized graphically and descriptively, as appropriate, by treatment group. They may include, but are not limited to:

- Absolute and relative changes from baseline in biomarkers at each sampling timepoint
- Relationships between change in biomarkers from baseline and efficacy measures and other biomarkers
- The relationship between biomarkers at baseline and clinical response

6.10 HEALTH STATUS UTILITY ANALYSES

The change from baseline in EQ-5D-5L health utility index-based and VAS scores will be calculated at specified timepoints.

6.11 INTERIM ANALYSIS

Periodic reviews of the safety data will be conducted by an iDCC with the results reviewed by the iDMC. A planned independent unblinded early review of the PK data from approximately 15 patients receiving satralizumab will be performed to confirm the adequacy of the chosen doses (see Section 6.11.2). The iDMC will then make a dose recommendation.

Details of these analyses will be described in the iDMC Charter.

6.11.1 Optional Interim Analysis

To adapt to information that may emerge during the course of this study, the Sponsor may choose to conduct one interim analysis for futility. Below are the specifications in place to ensure the study continues to meet the highest standards of integrity when an optional interim analysis is executed.

If an interim analysis is conducted, the Sponsor will remain blinded. The interim analysis will be conducted by an external statistical group and reviewed by the iDMC. Interactions between the iDMC and Sponsor will be carried out as specified in the iDMC Charter.

The decision to conduct the optional interim analysis, along with the rationale, timing, and statistical details for the analysis will be documented in the SAP. The iDMC Charter will be updated to document potential recommendations the iDMC can make to the Sponsor as a result of the analysis (e.g., continue the trial without modification, stop the study for futility).

The study will not be stopped for positive efficacy as a result of the interim analysis.

6.11.2 Interim Pharmacokinetic Analysis

An interim analysis of PK data *was* performed when approximately 30 patients, (*including* approximately 15 patients from the satralizumab group), completed a minimum of 8 weeks of DB treatment. The purpose of the interim analysis *was* to confirm that the achieved exposure to satralizumab (and predicted RO) *was* within the predicted range. Patients with gMG with body weights representative of the overall gMG population, both in terms of range and approximate proportion, *were* included in the PK interim analysis dataset.

A dose decision framework (including a pre-specified alternative higher dose, in case exposures are lower than predicted) *was* defined in an analysis plan prior to study start. This plan set out the criteria for predicted exposure and RO (derived using the existing pop PK model updated following incorporation of the new data in gMG) under which the decision for an adapted dose will be made.

This interim PK analysis *was* performed by an external contract research organization (CRO) while the Sponsor, patients, and investigators *remained* blinded. The review by the external CRO *was* restricted to PK and ADA data only, not safety or efficacy data, and no information that would reveal individual treatment assignments *was* shared with the Sponsor. The external CRO *performed* blinded simulations for exposure and RO, which *were* made available to the iDMC, and *collaborated* with the iDMC, such that the iDMC *made* a dose recommendation on the basis of these simulations. Following this review, the iDMC *recommended that the initially proposed doses (120 mg ≤100 kg >180 mg) should be retained and that* the Sponsor *should continue the study without dose modification.*

Study recruitment will continue during the review period. Should a dose change be warranted, any patients treated at the original dose level will continue in the study on randomized treatment at the revised dose level, but will not contribute to the primary analysis. Additional patients will be recruited to ensure that the number of patients eligible for inclusion in the primary analysis reaches the target sample size. No type I error multiplicity correction will be performed as only PK data, unrelated to efficacy outcome, will be used for interim decision-making.

6.12 CHINA SUBPOPULATION ANALYSES

The China subpopulation will include all patients enrolled at China's sites*: current resident of mainland* China*, Hong Kong, or Taiwan, and of Chinese ancestry*. Results from these analyses will be summarized in a separate Clinical Study Report.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of

eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data and other electronic data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

PRO and ClinRO data will be collected on paper questionnaires. The data from the questionnaires will be entered into the EDC system by site staff.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format that must be kept with the study records. Acknowledgement of receipt of the data is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, PROs, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic or paper PRO, ClinRO data, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

The Sponsor will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directives (2001/20/EC) or Clinical Trials Regulation (536/2014) and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as an Assent Form or Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

If the Consent Forms are revised (through an amendment or an addendum) while a patient is participating in the study, the patient or a legally authorized representative

must re-consent by signing the most current version of the Consent Forms or the addendum, in accordance with applicable laws and IRB/EC policy. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

In the event of a data security breach, appropriate mitigation measures will be implemented.

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Section 9.6).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

Study data, which may include data on genomic variants, may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and other summary reports will be provided upon request (see Section 9.6).

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.2).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 MANAGEMENT OF STUDY QUALITY

The Sponsor will implement a system to manage the quality of the study, focusing on processes and data that are essential to ensuring patient safety and data integrity. Prior to study initiation, the Sponsor will identify potential risks associated with critical trial processes and data and will implement plans for evaluating and controlling these risks. Risk evaluation and control will include the selection of risk-based parameters (e.g., adverse event rate, protocol deviation rate) and the establishment of quality tolerance limits for these parameters prior to study initiation. Detection of deviations from quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the establishment and monitoring of quality tolerance limits will be provided in a Quality Tolerance Limit Management Plan.

9.4 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.5 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to HCPs and to the public, at scientific congresses, in clinical trial

registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and/or other summaries of clinical study results may be available in health authority databases for public access, as required by local regulation, and *will* be made available upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical *Study Information* at the following website:

https://www.roche.com/innovation/process/clinical-trials/data-sharing/

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.6 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by F. Hoffmann–La Roche Ltd; Chugai Pharmaceutical Co., Ltd. is co-sponsor in Taiwan and Japan. The Sponsor will provide clinical operations management, data management, and medical monitoring.

Approximately 120 sites globally will participate to enroll *approximately 160 AChR+ patients and up to 25 MuSK+or LRP4+* patients. Enrollment will occur through an IxRS.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, biomarker, PK, and PD analyses), as specified in Section 4.5.

An iDMC will be employed to monitor and evaluate patient safety throughout the study.

9.7 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only.

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Appendix 1
Schedule of Activities: Screening and Double-Blind Periods

	Screening [a]	DB Tx Period								US Visit [b]	DD Visit [c]	RLD Visit 1,2,3 [d]	SFU Visit [e]	EOT Visit [f]
Weeks	–4 to –1	0	2	4	8	12	16	20	24					
Days	–28 to –1	1	15	29	57	85	113	141	169					
Window in days	NA	NA	±3	±3	±7	±7	±7	±7	±7				±7	±7
Informed consent [g]	x													
Review of inclusion/exclusion criteria	x	x												
Demographic data	x													
Medical history and baseline conditions	x													
Height	x	x [h]			x [h]		x [h]		x [h]	x [h]	x [h]	x [h]	x [h]	x [h]
Body weight	x	x			x		x		x	x	x	x	x	x
Study drug administration		x	x	x	x	x	x	x			x	x		
Complete Physical examination [i]	x	x				x			x			x [j]	x	x
Limited Physical examination [i]			x	x	x		x	x		x	x	x [k]		
Vital signs [l]	x	x	x	x	x	x	x	x	x	x	x	x	x	x
12-Lead ECG [m]	x	x				x			x	x		x [j]		x
Hematology [n,o]	x	x	x	x	x	x	x	x	x	x	x [p]	x	x	x
Chemistry [o,q]	x	x	x	x	x	x	x	x	x	x	x [p]	x	x	x
Fibrinogen, INR [o]	x	x	x	x	x	x	x	x	x	x	x [p]	x	x	x

Appendix 1:Schedule of Activities: Screening and Double-Blind Periods (cont.)

	Screening [a]	DB Tx Period								US Visit [b]	DD Visit [c]	RLD Visit 1,2,3 [d]	SFU Visit [e]	EOT Visit [f]
Weeks	–4 to –1	0	2	4	8	12	16	20	24					
Days	–28 to –1	1	15	29	57	85	113	141	169					
Window in days	NA	NA	±3	±3	±7	±7	±7	±7	±7				±7	±7
Pregnancy test [r, s]	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Urinalysis [t]	x	x	x	x	x	x	x	x	x	x	x [p]	x	x	
TB screening [u,s]	x													
Hepatitis test [v]	x													
Hepatitis B viral DNA (if required) [s, v]	x					x			x				x	x
TBNK [o]	x	x				x			x	x		x	x	x
Quantitative Igs [o, s, w]	x	x				x			x			x [j]	x	x
IgG subclasses [o, s, x]	x	x				x			x			x [j]	x	x
C–SSRS		x	x	x	x	x	x	x	x	x		x		x
Concomitant medications [y]	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events [z]	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Efficacy [aa]														
MG-ADL	x	x	x	x	x	x	x	x	x	x		x		x
QMG	x	x	x	x	x	x	x	x	x	x		x		x
MGC	x	x	x	x	x	x	x	x	x	x		x		x
MG-QOL 15r	x	x		x	x	x	x	x	x	x		x		x

Appendix 1:Schedule of Activities: Screening and Double-Blind Periods (cont.)

	Screening [a]	DB Tx Period								US Visit [b]	DD Visit [c]	RLD Visit 1,2,3 [d]	SFU Visit [e]	EOT Visit [f]
Weeks	–4 to –1	0	2	4	8	12	16	20	24					
Days	–28 to –1	1	15	29	57	85	113	141	169					
Window in days	NA	NA	±3	±3	±7	±7	±7	±7	±7				±7	±7
NeuroQoL Fatigue Subscale	x	x		x	x	x	x	x	x	x		x [bb]		x
EuroQoL EQ-5D-5L		x							x			x [j]		x
PK and biomarkers														
PK sample [o]		x	x	x	x	x	x	x	x	x	x	x	x	x
PD sample [o, cc]	x [s]	x	x	x	x	x	x	x	x	x	x	x	x	x
Blood sample for RNA [o, dd, ee]		x				x			x	x		x [j]	x	x
Blood sample for flow cytometry [o, ee, ff,]	x	x				x			x	x		x	x	x
Screening serum sample for autoantibodies [o, s, gg]	x													
Serum sample for biomarkers [o, s, hh]	x	x	x	x	x	x	x	x	x	x		x	x	x
PBMC sample [o, ee, ii]	x	x				x			x			x [j]	x	x
Blood sample for DNA [jj]		x												

Appendix 1:Schedule of Activities: Screening and Double-Blind Periods (cont.)

	Screening [a]	DB Tx Period								US Visit [b]	DD Visit [c]	RLD Visit 1,2,3 [d]	SFU Visit [e]	EOT Visit [f]
Weeks	–4 to –1	0	2	4	8	12	16	20	24					
Days	–28 to –1	1	15	29	57	85	113	141	169					
Window in days	NA	NA	±3	±3	±7	±7	±7	±7	±7				±7	±7
Immunogenicity [o]														
ADA sample		x	x	x	x	x	x	x	x	x	x	x	x	x
RBR														
Serum sample for RBR (optional) [o, ee, kk]		x				x			x				x	x
Plasma sample for RBR (optional) [o, ee, kk]		x				x			x				x	x

AChR = acetylcholine receptor; ADA = anti-drug antibody; β–hCG = β–human chorionic gonadotropin; Ca = calcium; Cl = chlorine; CRP = C-reactive protein; C–SSRS = Columbia Suicide Severity Scale; DB = double-blind; DD = delayed dosing; EC = Ethics Committee; eCRF = electronic Case Report Form; EOT = end of treatment/treatment discontinuation; GGT = gamma-glutamyl transferase; *gMG = generalized myasthenia gravis;* HBcAb = hepatitis B core antibody ; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCVAb = hepatitis C virus antibody; IL-6 = interleukin-6; IL-17 = interleukin-17; IRB = Institutional Review Board; K = potassium; LRP4 = low-density lipoprotein receptor–related protein 4; MG-ADL = Myasthenia Gravis Activities of Daily Living; MGC = Myasthenia Gravis Composite ; MG-QOL 15r = Myasthenia Gravis Quality of Life 15 Scale (revised); MuSK = muscle-specific kinase; NA = not applicable; Neuro–QoL = Quality of Life in Neurological Disorders; P = phosphorus; PBMC = peripheral blood mononuclear cell; PD = pharmacodynamic; PK = pharmacokinetic; Q4W = every 4 weeks; QMG = Quantitative Myasthenia Gravis; QOL = quality of life; RBR = Research Biosample Repository; *RLD = re-loading dose*; SFU = safety follow-up; sIL-6R = soluble interleukin-6 receptor; TB = tuberculosis; TBNK = T-, B-, and natural killer cells; Tx = treatment; US = unscheduled; WD = withdrawal; WGS = whole genome sequencing

[a] Visit not specified by the protocol.

[b] Unscheduled visit: Assessments performed at unscheduled (non-dosing) visits will depend on the clinical needs of the patient. In case of suspected gMG exacerbation the patient should undergo the following evaluations before or immediately after any administration of the rescue therapy: MG-ADL, QMG, MGC, and MG-QOL 15r. Additional assessments, such as hematology, chemistry, and urinalysis, will be performed if infection or metabolic disturbance is suspected to be contributing to the clinical presentation necessitating the unscheduled visit.

[c] In the event that the study drug is not administered within the scheduled visit window and is subsequently administered outside the visit window. Minimum dosing interval should be 8 days for loading doses and 14 days for maintenance doses.

[d] Re-loading doses 1 and 2 are needed for drug interruption for a duration between 8 to 12 weeks. Re-loading doses 1, 2, and 3 are needed for a drug interruption longer than 12 weeks, inclusive (see Section 4.3.2.2, Table 7).

[e] All patients who permanently discontinue study treatment during the DB period for any reason should continue with all remaining assessments defined in the protocol. However, at a minimum, patients who are unwilling to return to the clinic for all assessments will be asked to complete SFU visits. For adults, a SFU visit is required 12 weeks after the final dose. For adolescents, SFU visits are required 12 weeks and 24 weeks after the final dose. For all patients, a telephone interview will be conducted by site personnel every 4 weeks after the final dose until the final SFU visit to identify any new or worsening neurological symptoms.

[f] An EOT visit will be performed for patients who permanently discontinue from satralizumab treatment in this study. The EOT visit should be conducted at time of discontinuation, within 4 weeks after the final dose. At this visit a complete set of assessments will be conducted. If the EOT coincides with a scheduled visit, the EOT visit should be completed instead of the scheduled visit.

[g] Must be obtained and documented in written form before any study-specific screening procedure and initiation of study treatment.

[h] Height should be measured for adolescent patients (aged $\geq$ 12 years to $<$ 18 years).

[i] Perform a complete physical examination at screening and other specified visits that should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems (see Section 4.5.4). Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. During the study conduct, perform a limited, symptom-directed examination at specified timepoints or as clinically indicated. Record changes from baseline in patient notes. Record new or worsened clinically significant abnormalities as adverse events on the Adverse Event eCRF.

[j] These assessments only apply to RLD Visit 1.

[k] These assessments only apply to RLD Visits 2 and 3.

[l] Includes body temperature, respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position. Vital signs are measured just before dosing and 15 ($\pm$ 5) minutes and 60 ($\pm$ 5) minutes after dosing for the first 5 doses in case of study drug injection visit. Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions.

[m] ECG should be performed prior to blood draws.

[n] Hematology includes hemoglobin, hematocrit, RBC, WBC (absolute and differential: neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells), quantitative platelet count.

[o] All clinical laboratory, PK, PD, biomarker, and ADA samples should be obtained pre-dose at indicated visits. Samples should be taken in the morning if possible, and approximately at the same time across visits.

[p] If study drug was not administered on schedule because of a safety issue with laboratory abnormality, then the relevant laboratory parameter should be tested at the DD Visit.

[q] Chemistry includes albumin, total protein, total bilirubin, ALP, AST, ALT, GGT, LDH, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, ferritin, BUN, creatinine, sodium, Cl, K, Ca, P, complements (CH50, C3, C4), lipase, CRP, serum CK, *and uric acid*.

[r] All female patients of childbearing potential will have a serum pregnancy test at screening. Urine pregnancy tests will be performed pre-dose at specified subsequent visits. If a urine pregnancy test is positive, the patient will not receive the scheduled dose, and a confirmatory serum pregnancy test will be performed. Urine β–hCG (sensitivity of at least 25 mU/mL) will be performed locally.

[s] For adolescent patients testing/sampling procedures will be adjusted in conformance with guidelines for pediatric blood volume limits from health authorities. Please refer to the laboratory manual for detailed instructions.

[t] Samples for clinical laboratory tests should be collected pre-dose on dosing days. If any abnormalities are detected on urine dipstick tests (including urinary glucose, urinary protein, urinary occult blood, urobilinogen), a complete urinalysis (including microscopic of examination of urine) and/or urine culture is to be performed as deemed necessary.

[u] A TB test (e.g., tuberculin test and/or Quantiferon® test) should be conducted according to local guidance. If the patient is positive for latent TB, then the patient must be treated with appropriate anti-mycobacterial therapy for at least 4 weeks prior to initiating study treatment administration. Additional tests for the diagnosis of latent and active TB should be done as per the local guidance, including a chest X-ray or chest CT, in addition to the TB tests in individuals with a positive TB test or in individuals who have a potential risk for TB infection/TB reactivation (e.g., on immunosuppressive therapies, recently in contact with a person who has infectious TB disease, live in or recently traveled to a high-prevalence region/countries).

[v] HBsAg, HBcAb, HBsAb, HCVAb: All patients must have negative HBsAg test result at screening prior to enrollment.
Hepatitis B screening: Patients who are HBsAg positive will be excluded from the study. If HBcAb status is positive, hepatitis B viral DNA will be measured. If HBV DNA is detectable, the individual must be excluded. If HBV DNA is undetectable, the individual may be enrolled. In these participants, HBV DNA measurement must be performed regularly at 12 weekly intervals during the study.
Hepatitis C screening: If HCVAb is positive, HCV RNA will be measured. If HCV RNA is undetectable ≥12 weeks after HCV treatment completion, the patient can be enrolled.

[w] Quantitative immunoglobulins may include IgA, IgE, IgG, and IgM.

[x] IgG subtypes include IgG1, IgG2, IgG3 and IgG4.

[y] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment.

[z] All adverse events will be reported for as long as the patient remains in the study. Serious adverse event reporting starts with signing of the Informed Consent Form. The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or to trial-related procedures until a final outcome can be reported.

[aa] Efficacy assessments must be performed prior to dosing and prior to any other assessments, preferably at the same time in the morning across all visits.

[bb] These assessments only apply to RLD Visits 1 and 3.

[cc] PD biomarkers will include, but are not limited to, IL-6 and sIL-6R.

[dd] RNA may be assessed for exploratory biomarkers including, but not limited to, plasmablast signature.

[ee] For adolescent patients at the time of informed consent, this sample is not to be collected.

[ff] Blood samples will be processed for flow cytometry (e.g., B-cell subsets).

[gg] Autoantibodies will include AChR, MuSK and LRP4. *Note that for sites in the Netherlands and Germany, the central laboratory autoantibody tests at screening to confirm gMG diagnosis are not required.*

[hh] Exploratory serum biomarkers may include, but will not be limited to autoantibodies (AChR, MuSK, and LRP4) and IL-17.

[ii] Plasma generated from the blood sample obtained for PBMC processing will be stored for biomarker research. No additional blood draw is needed.

[jj] A single mandatory DNA sample will be collected for patient genotyping at the baseline visit. If the DNA sample is not collected at the baseline visit, it may be collected at any subsequent visit. Collection and submission of this sample is contingent upon the review and approval of the exploratory research by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for WGS sampling, collection of this sample will not be applicable at that site.

[kk] These sample types to be collected for research purposes if a patient signs the Optional RBR Informed Consent Form.

Appendix 2
Schedule of Activities: Open-Label Extension Period

	Screening [a]	From Week 0 to Week 24								After Week 24				US Visit	DD Visit[b]	RLD Visit 1,2,3 [c]	EOT Visit[d]	SFU/ EOS Visit [e]
Week	*–4 to –1*	0[f,g]	2	4	8	12	16	20	24	Q4W[h]	Q12W	Q24W	Q48W					
Window in days	*NA*	NA	±3	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7				±7	±7
Informed Consent [i]	*x*																	
Review of inclusion/ exclusion criteria	*x*	*x* [a]																
Demographic Data	*x*																	
Medical history and baseline conditions	*x*																	
Study drug administration		x	x	x	x	x	x	x	x	x	x	x	x		x	x		
Height	*x*					x [j]			x [j]		x [j]	x [j]	x [j]					
Body weight	*x*	x				x			x		x	x	x		x	x	x	x
Complete physical examination[k]	*x*	x				x			x			x	x			x [l]	x	x
Limited physical examination[k]			x	x	x		x	x			x [m]			x	x	*x*[n]		

Appendix 2:Schedule of Activities: Schedule of Activities: Open-Label Extension Period (cont.)

	Screening [a]	From Week 0 to Week 24								After Week 24				US Visit	DD Visit[b]	RLD Visit 1,2,3 [c]	EOT Visit[d]	SFU/ EOS Visit [e]
Week	*−4 to −1*	0[f,g]	2	4	8	12	16	20	24	Q4W[h]	Q12W	Q24W	Q48W					
Window in days	*NA*	NA	±3	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7				±7	±7
Vital signs [o]	*x*	x	x	x	x	x	x	x	x		x	x	x	x	x	x	x	x
12-Lead ECG [p]	*x*	x				x			x			x	x	x		x[l]	x	x
Hematology [q,r]	*x*	x	x	x	x	x	x	x	x		x	x	x	x	x [s]	x	x	x
Chemistry [t, r]	*x*	x	x	x	x	x	x	x	x		x	x	x	x	x [s]	x	x	x
Fibrinogen, INR [r]	*x*	x	x	x	x	x	x	x	x		x	x	x	x		x	x	x
Cortisol [u]						x			x		x	x	x		x		x	x
Low-dose ACTH stimulation test [u]						x			x		x	x	x		x		x	x
Pregnancy test [v]	*x*	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x	x
Urinalysis [w]	*x*	x	x	x	x	x	x	x	x		x	x	x	x		x	x	x
TBNK [r]	*x*	x				x			x				x	x		x	x	x
TB screening [x,y]	*x*																	
Quantitative Igs [r, y, z]	*x*	x				x			x				x			x [l]	x	x
C–SSRS		x	x	x	x	x	x	x	x		x	x	x	x		x	x	x

Appendix 2:Schedule of Activities: Schedule of Activities: Open-Label Extension Period (cont.)

	Screening[a]	From Week 0 to Week 24								After Week 24				US Visit	DD Visit[b]	RLD Visit 1,2,3[c]	EOT Visit[d]	SFU/ EOS Visit [e]
Week	*−4 to −1*	0[f,g]	2	4	8	12	16	20	24	Q4W[h]	Q12W	Q24W	Q48W					
Window in days	*NA*	NA	±3	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7				±7	±7
IgG subclasses [r, y, aa]	*x*	x				x			x				x			x [l]	x	x
Hepatitis Test[bb]	*x*																	
Hepatitis B viral DNA [cc]	*x*	x				x			x		x	x	x	x		x	x	x
Concomitant medications	*x*	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events	*x*	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Record if any changes in background therapy [dd]				x	x	x	x	x	x		x	x	x		x		x	x
Efficacy																		
MG-ADL	*x*	x	x	x	x	x	x	x	x			x	x	x		x	x	
QMG	*x*	x	x	x	x	x	x	x	x			x	x	x		x	x	
MGC	*x*	x	x	x	x	x	x	x	x			x	x	x		x	x	
MG-QOL 15r (revised)	*x*	x	x	x	x	x	x	x	x			x	x	x		x	x	
NeuroQoL Fatigue Subscale	*x*	x	x	x	x	x	x	x	x			x	x			x [ee]	x	
EuroQoL EQ-5D-5L		x										x	x			x [l]	x	

Appendix 2:Schedule of Activities: Schedule of Activities: Open-Label Extension Period (cont.)

	Screening[a]	From Week 0 to Week 24								After Week 24				US Visit	DD Visit[b]	RLD Visit 1,2,3[c]	EOT Visit[d]	SFU/ EOS Visit [e]
Week	*−4 to −1*	0[f,g]	2	4	8	12	16	20	24	Q4W[h]	Q12W	Q24W	Q48W					
Window in days	*NA*	NA	±3	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7				±7	±7
PK and biomarkers																		
PK sample [r]		x	x	x	x	x	x	x	x		x	x	x	x	x	x	x	x
PD sample [r, ff]	*x* [y]	x	x	x	x	x	x	x	x		x	x	x	x	x	x	x	x
Blood sample for RNA [r,gg, hh]		x				x			x				x	x		x [l]	x	x
Blood sample for DNA [a, ii]		*x*																
Blood sample for flow cytometry [r, hh, jj]	*x*	x				x			x				x	x		x	x	x
Screening serum sample for autoantibodies [r,y,kk]	*x*																	
Serum sample for biomarkers [r, y, ll]	*x*	x		x	x	x	x	x	x				x	x		x	x	x
PBMC sample [r, hh, mm]	*x*	x				x			x				x			x [l]	x	x
Immunogenicity [r]																		
ADA sample		x	x	x	x	x	x	x	x		x	x	x	x	x	x	x	x

Appendix 2:Schedule of Activities: Schedule of Activities: Open-Label Extension Period (cont.)

	Screening[a]	From Week 0 to Week 24								After Week 24				US Visit	DD Visit[b]	RLD Visit 1,2,3[c]	EOT Visit[d]	SFU/ EOS Visit [e]
Week	*–4 to –1*	0[f,g]	2	4	8	12	16	20	24	Q4W[h]	Q12W	Q24W	Q48W					
Window in days	*NA*	NA	±3	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7				±7	±7
RBR																		
Serum sample for RBR (optional) [r, hh, nn]		x				x			x				x				x	x
Plasma sample for RBR (optional) [r, hh, nn]		x				x			x				x				x	x

AChR=acetylcholine receptor; ACTH=adrenocorticotropic hormone; ADA=anti-drug antibody; AS=adrenal suppression; β–hCG=β–human chorionic gonadotropin; Ca=calcium; Cl=chlorine; CRP=C-reactive protein; C-SSRS=Columbia Suicide Severity Scale; *CT=computed tomography;* DB=double-blind; DD=delayed dosing; *EC=Ethics Committee; eCRF=electronic Case Report Form;* EOS=end of study; EOT=end of treatment; GGT=gamma-glutamyl transferase; *gMG=generalized myasthenia gravis;* HBcAb=hepatitis B core antibody ; HBsAb=hepatitis B surface antibody; *HBsAg=hepatitis B surface antigen;* HBV=hepatitis B virus; *HCV=hepatitis C virus*; HCVAb=hepatitis C virus antibody; HPA=hypothalamus-pituitary-adrenal; IL-6=interleukin-6; IL-17=interleukin-17; *IRB=Institutional Review Board;* IST=immunosuppressant; K=potassium; LRP4=low-density lipoprotein receptor–related protein 4; MG-ADL=Myasthenia Gravis Activities of Daily Living; MGC=Myasthenia Gravis Composite; MG-QOL 15r=Myasthenia Gravis Quality of Life 15 Scale (revised); MuSK=muscle-specific kinase; NA=not applicable; Neuro–QoL=Quality of Life in Neurological Disorders; OLE=open-label extension; P=potassium; PBMC=peripheral blood mononuclear cell; PD=pharmacodynamic; PK =pharmacokinetic; Q4W=every 4 weeks; Q12W=every 12 weeks; Q24W=every 24 weeks; Q48W=every 48 weeks; QMG=Quantitative Myasthenia Gravis; QoL=quality of life; RBR=Research Biosample Repository; RLD=re-loading dose; sIL-6R=soluble interleukin-6 receptor; SFU=safety follow up; *TB=tuberculosis;* TBNK=T, B, and natural killer cells; US=unscheduled; *WGS=whole genome sequencing*.

[a] *Applicable only to adolescent patients who first enter the study in the OLE period because screening would not have been completed previously. Visit is not specified by the protocol.*

[b] In the event that the study drug is not administered within the scheduled visit window and is subsequently administered outside the visit window. The minimum dosing interval should be 14 days.

[c] RLDs 1 and 2 are needed for drug interruption for a duration between 8 to 12 weeks. RLDs 1, 2, and 3 are needed for a drug interruption longer than 12 weeks, inclusive.

[d] An EOT visit will be performed for all patients who permanently discontinue treatment during the OLE period and who continue treatment with satralizumab outside of this study. At this visit a complete set of assessments will be conducted. If the EOT visit coincides with a scheduled visit, the EOT visit should be completed instead of the scheduled visit.

[e] Adult patients will be asked to complete a SFU visit 12 weeks after the final dose of satralizumab. Adolescent patients will be asked to complete SFU visits 12 weeks and 24 weeks after the final dose of satralizumab. Patients who decide to continue treatment with satralizumab outside of this study will have to complete the EOT visit, but they will not have to complete the SFU nor the EOS visit.

[f] *For adult and adolescent patients who complete the DB period,* Week 0 visit of the OLE period coincides with the final visit of the DB period. The assessments performed at Week 24 (final week) of the DB period will be used as the active treatment baseline for the patients who receive placebo during the DB period and as the OLE baseline for patients who receive satralizumab during the DB period. Duplicate assessments should be avoided.

[g] *For adolescent patients who do not complete the DB period and transition to the OLE period, the assessments performed at the visit at which they receive the first active treatment will be used as the active treatment baseline.*

[h] In accordance with local regulations, administration of satralizumab outside of the study site (home treatment) is allowed. Patients should be followed up by study site personnel through phone calls around the scheduled study drug administration dates to monitor compliance, concomitant medications, and adverse events.

[i] *Must be obtained and documented in written form before any study-specific screening procedure and initiation of study treatment.*

[j] Height should be measured for adolescent patients (*aged ≥12 years to <18 years).*

[k] *Perform a complete physical examination at screening and other specified visits that should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems (see Section 4.5.4). Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. During the study conduct, perform a limited, symptom-directed examination at specified timepoints or as clinically indicated. Record changes from baseline in patient notes. Record new or worsened clinically significant abnormalities as adverse events on the Adverse Event eCRF.*

[l] These assessments only apply to RLD D Visit 1.

[m] Limited physical examination will be performed Q12W and during the re-loading dose visits except on visits when a complete physical examination will be performed.

[n] *Applicable only for RLD Visits 2 and 3.*

[o] Includes body temperature, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position. Vital signs are measured just before dosing and 15 (± 5) minutes and 60 (± 5) minutes after dosing for the first 5 OLE doses in case of study drug injection visit. Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions.

[p] ECG should be performed prior to blood draws.

[q] Hematology includes hemoglobin, hematocrit, RBC, WBC (absolute and differential: neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells), quantitative platelet count.

[r] All clinical laboratory, PK, PD, ADA, and biomarker samples should be obtained pre-dose at indicated visits. Samples should be taken in the morning if possible, and approximately at the same time across visits.

[s] If study drug was not administered on schedule because of a safety issue with laboratory abnormality, then the relevant laboratory parameter should be tested at the DD Visit.

[t] Chemistry includes albumin, total protein, total bilirubin, ALP, AST, ALT, GGT, LDH, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, ferritin, BUN, creatinine, sodium, Cl, K, Ca, P, complements (CH50, C3, C4), lipase, CRP, serum CK*, and uric acid*.

[u] For patients on the corticosteroid taper with symptoms of AS early morning cortisol has to be measured. If morning cortisol is normal, but patient has symptoms of AS, perform low-dose ACTH stimulation test to confirm AS diagnosis.

[v] Urine pregnancy tests will be performed at specified visits. If a urine pregnancy test is positive, the patient will not receive the scheduled dose, and a confirmatory serum pregnancy test will be performed. Urine β–hCG (sensitivity of at least 25 mU/mL) will be performed locally. *All female adolescent patients of childbearing potential who enter directly in the OLE will have a serum pregnancy test at screening.*

[w] Samples for clinical laboratory tests should be collected pre-dose on dosing days. If any abnormalities are detected on urine dipstick tests (including urinary glucose, urinary protein, urinary occult blood, urobilinogen), a complete urinalysis (including microscopic of examination of urine) and/or urine culture is to be performed as deemed necessary.

[x] *A TB test (e.g., tuberculin test and/or Quantiferon® test) should be conducted according to local guidance. If the patient is positive for latent TB, then the patient must be treated with appropriate anti-mycobacterial therapy for at least 4 weeks prior to initiating study treatment administration. Additional tests for the diagnosis of latent and active TB should be done as per the local guidance, including a chest X-ray or chest CT, in addition to the TB tests in individuals with a positive TB test or in individuals who have a potential risk for TB infection/TB reactivation (e.g., on immunosuppressive therapies, recently in contact with a person who has infectious TB disease, live in or recently traveled to a high-prevalence region/countries).*

[y] For adolescent patients testing/sampling procedures will be adjusted in conformance with guidelines for pediatric blood volume limits from health authorities. Please refer to the laboratory manual for detailed instructions.

[z] Quantitative immunoglobulins may include IgA, IgE, IgG and IgM.

[aa] IgG subtypes include IgG1, IgG2, IgG3 and IgG4.

[bb] *HBsAg, HBcAb, HBsAb, HCVAb: All patients must have negative HBsAg test result at screening prior to enrollment.*
Hepatitis B screening: Patients who are HBsAg positive will be excluded from the study. If HBcAb status is positive, hepatitis B viral DNA will be measured. If HBV DNA is detectable, the individual must be excluded. If HBV DNA is undetectable, the individual may be enrolled. In these participants, HBV DNA measurement must be performed regularly at 12 weekly intervals during the study.
Hepatitis C screening: If HCVAb is positive, HCV RNA will be measured. If HCV RNA is undetectable ³ 12 weeks after HCV treatment completion, the patient can be enrolled.

[cc] Hepatitis B viral DNA must be monitored every 12 weeks in patients whose HBcAb is positive and HBV DNA was negative at screening.

[dd] Change in background therapy is allowed after Week 12 in the OLE period to ensure patients treated with placebo in the DB period have reached steady-state levels of satralizumab prior to steroid or IST taper.

[ee] These assessments only apply to RLD Visits 1 and 3.

[ff] PD measurements will include, but not be limited to IL-6 and sIL-6R.

[gg] RNA may be assessed for exploratory biomarkers including, but not limited to, plasmablast signature.

[hh] For adolescent patients (at the time of informed consent) this sample is not to be collected.

[ii] *A single mandatory DNA sample will be collected for patient genotyping at the baseline visit. If the DNA sample is not collected at the baseline visit, it may be collected at any subsequent visit. Collection and submission of this sample is contingent upon the review and approval of the exploratory research by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for WGS sampling, collection of this sample will not be applicable at that site.*

[jj] Blood samples will be processed for flow cytometry (e.g., B-cell subsets).

[kk] *Autoantibodies will include AChR, MuSK and LRP4. Note that for sites in the Netherlands and Germany, the central laboratory autoantibody tests at screening to confirm gMG diagnosis are not required.*

[ll] Exploratory serum biomarkers may include but not be limited to autoantibodies (AChR, MuSK and LRP4) and IL-17.

[mm] Plasma sample will also be collected at all visits following PBMC sample processing and will be stored for biomarker research.

[nn] Sample types to be collected for research purposes if a patient signs the Optional RBR Informed Consent Form.

Appendix 3
Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples

Visit	Timepoint	Instructions	Sample Type
Screening	Weeks −4 to −1	—	• Biomarker (PD serum) • Biomarker (serum) • Biomarker (flow cytometry) • Biomarker (PBMCs) • Autoantibodies (serum) [a]
DB	Weeks 0 to 24	Only at Week 0	• Biomarker (DNA)
		Prior to each administration of satralizumab	• PK sample (serum) • Biomarker (PD serum) • Anti-satralizumab antibodies (serum) • Biomarker (serum)
		Prior to administration of satralizumab, Q12W	• Biomarker (flow cytometry) • Biomarker (PBMCs) • Biomarker (optional RBR serum) • Biomarker (optional RBR plasma) • Biomarker (RNA)
OLE	Weeks 0 to 24	Prior to administration of satralizumab for Week 0, 2 and 4, then prior to each administration of satralizumab, Q4W	• PK sample (serum) • Biomarker (PD serum) • Anti-satralizumab antibodies (serum)
		Prior to each administration of satralizumab, Q4W	• Biomarker (serum)
		Prior to each administration of satralizumab, Q12W	• Biomarker (flow cytometry) • Biomarker (PBMCs) • Biomarker (optional RBR serum) • Biomarker (optional RBR plasma) • Biomarker (RNA)

Visit	Timepoint	Instructions	Sample Type
OLE (cont.)	After Week 24	Prior to administration of satralizumab, Q12W	• PK sample (serum) • Biomarker (PD serum) • Anti-satralizumab antibodies (serum)
		Prior to administration of satralizumab, Q48W	• Biomarker (flow cytometry) • Biomarker (PBMCs) • Biomarker (RNA) • Biomarker (serum) • Biomarker (optional RBR serum) • Biomarker (optional RBR plasma)
Unscheduled visit	—	—	• PK sample (serum) • Biomarker (PD serum) • Anti-satralizumab antibodies (serum) • Biomarker (flow cytometry) • Biomarker (RNA) • Biomarker (serum)
DD	—	—	• PK sample (serum) • Biomarker (PD serum) • Anti-satralizumab antibodies (serum)
RLD (visit 1)	—	—	• PK sample (serum) • Biomarker (PD serum) • Anti-satralizumab antibodies (serum) • Biomarker (RNA) • Biomarker (flow cytometry) • Biomarker (serum) • Biomarker (PBMCs)
RLD (visit 2 and 3)	—	—	• PK sample (serum) • Biomarker (PD serum) • Anti-satralizumab antibodies (serum) • Biomarker (flow cytometry) • Biomarker (serum)

Visit	Timepoint	Instructions	Sample Type
EOT and SFU	—	—	• PK sample (serum) • Biomarker (PD serum) • Anti-satralizumab antibodies (serum) • Biomarker (RNA) • Biomarker (flow cytometry) • Biomarker (serum) • Biomarker (PBMCs) • Biomarker (optional RBR serum) • Biomarker (optional RBR plasma)

DB = double-blind; DD = delayed dosing; EOT = end of treatment; FU = follow-up; OLE = open-label extension; PBMC = peripheral blood mononuclear cell; PD = pharmacodynamic; PK = pharmacokinetic; Q4W = every 4 weeks; Q12W = every 12 weeks; Q24W = every 24 weeks; Q48W = every 48 weeks; RBR = Research Biosample Repository; RLD = re-loading dose SFU = safety follow-up.

[a] *For sites in the Netherlands and Germany, the central laboratory autoantibody tests at screening to confirm gMG diagnosis are not required.*

Appendix 4
Anaphylaxis Precautions

These guidelines are intended as a reference and should not supersede pertinent local or institutional standard operating procedures.

REQUIRED EQUIPMENT AND MEDICATION

The following equipment and medication are needed in the event of a suspected anaphylactic reaction during study treatment infusion:

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for SC, intramuscular, intravenous, and/or endotracheal administration in accordance with institutional guidelines
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

In the event of a suspected anaphylactic reaction during study treatment infusion, the following procedures should be performed:

1. Stop the study treatment infusion.
2. Call for additional medical assistance.
3. Maintain an adequate airway.
4. Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring if possible.
5. Administer antihistamines, epinephrine, or other medications and IV fluids as required by patient status and as directed by the physician in charge.
6. Continue to observe the patient and document observations.
7. Collect serum samples for immunogenicity testing.
8. Ask the patient to return for immunogenicity sample collection at the time of washout, if appropriate.

Appendix 5
Instructions for Tuberculosis Screening and Treatment

INTERPRETATION OF TUBERCULOSIS SCREENING RESULTS

Immunosuppressant biologic treatments have been shown to increase the risk of tuberculosis (TB) infection or to cause conversion from latent to active TB in some circumstances. Because of this, patients must be screened for active or latent TB prior to entry to this study.

DEFINITIONS

Active TB is a disease caused by *Mycobacterium tuberculosis* in any part of the body and that is in an active state as determined by either a smear or culture taken from any source which tests positive for TB or if there is radiographic evidence of TB. Individuals with active TB are symptomatic, depending upon the location of the disease (most commonly in the lungs but also possibly in the brain, kidneys, spine or elsewhere) and can spread the infection to others.

Diagnosis of latent TB is established when an individual is infected with *M. tuberculosis,* as evidenced by a positive tuberculin skin test (TST) or interferon gamma release assay (IGRA; e.g., QuantiFERON-TB Gold In-Tube assay) but is asymptomatic and has no evidence of active infection on screening pathology or radiographic tests. Such individuals do not pass the disease to others. Appropriate anti-mycobacterial therapy must start for such individuals at least 4 weeks before initiating study drug administration in this study, because the effect of anti-mycobacterial therapy may not appear immediately after initiating.

Tuberculosis Screening

TB screening must be performed prior to initiation of study drug treatment. TB screening should be conducted per local guidance. For reference, the U.S. Centers for Disease Control's (CDC) notes on TB testing may be found at http://www.cdc.gov/TB/TOPIC/testing/default.htm.

- As part of recording the patient's medical history, the patient will be asked if he or she has had either active or latent TB and whether the patient has received a Bacille Calmette–Guérin (BCG) vaccination. The patient will also be asked if he or she has been in contact with any individuals known to have active TB.
- TB test (e.g., TST [using purified protein derivative] and/or IGRA [e.g., Quantiferon-TB Gold]) is required at screening.

A chest X-ray or chest CT should be performed in individuals with a positive TB test or in individuals who have a potential risk for TB infection /TB reactivation (e.g., on immunosuppressive therapies, recently in contact with a person who has infectious TB disease, live in or recently traveled to a high-prevalence region/countries).

Additional diagnostic tests should be done, as recommended per the local guidance, in individuals with a positive TB test or in individuals who have a potential risk for TB infection /TB reactivation (e.g., on immunosuppressive therapies, recently in contact with a person who has infectious TB disease, live in or recently traveled to a high-prevalence region/countries).

Notes:

1. The TST may be positive if the patient has had a BCG vaccination or has been infected with TB in the past; IGRA results may also be positive in some cases of past infection.
2. Positive results of the TST and IGRA test may be reduced by immune suppression.
3. Local guidance may vary depending upon the sensitivity of strains of Mycobacterium tuberculosis present locally.

In case of any doubt as to the diagnosis of latent TB, it is advised that a local physician with expertise in the treatment of TB or the Medical Monitor is consulted.

A combination of the medical history, the results of the TST test and/or IGRA test*, other diagnostic tests recommended as per local guidance,* and any other investigations deemed appropriate by the Investigator on the basis of clinical signs and symptoms indicative of TB infection elsewhere in the body will be used by the investigator to determine study eligibility at screening for this study.

TB Treatment

If the patient is positive for latent TB, then appropriate anti-mycobacterial therapy must start for the patient at least 4 weeks before initiating study drug administration in this study, because the effect of anti-mycobacterial therapy may not appear immediately after initiating. Treatment regimens should be followed by the local guidance. If no local guidance exists for treatment of immunocompromised individuals, then the U.S. CDC's guidance must be followed (http://www.cdc.gov/TB/publications/LTBI/default.htm).

In case of any doubt as to the appropriate course of anti-mycobacterial therapy of latent TB, it is advised that a local physician with expertise in the treatment of TB or the Medical Monitor is consulted.

Management of signs/symptoms of TB during the study

If new signs/symptoms of TB infection develop during the study, perform diagnostic tests as above. If TB infection is diagnosed, interrupt study drug and consult the Medical Monitor. Report TB infection as a "Selected Adverse Event" (see Section 5.2.4).

Appendix 6
Myasthenia Gravis-Activities of Daily Living

Grade	0	1	2	3	Score
Talking	Normal	Intermittent slurring or nasal speech	Constant slurring or nasal, but can be understood	Difficult to understand speech	
Chewing	Normal	Fatigue with solid food	Fatigue with soft food	Gastric tube	
Swallowing	Normal	Rare episode of choking	Frequent choking necessitating changes in diet	Gastric tube	
Breathing	Normal	Shortness of breath with exertion	Shortness of breath at rest	Ventilator dependence	
Impairment of ability to brush teeth or comb hair	None	Extra effort, but no rest periods needed	Rest periods needed	Cannot do one of these functions	
Impairment of ability to arise from a chair	None	Mild, sometimes uses arms	Moderate, always uses arms	Severe, requires assistance	
Double vision	None	Occurs, but not daily	Daily, but not constant	Constant	
Eyelid droop	None	Occurs, but not daily	Daily, but not constant	Constant	

Total Score _____

Appendix 7
Quantitative Myasthenia Gravis

QMG form

Test Item	None	Mild	Moderate	Severe	Score	
Grade	**0**	**1**	**2**	**3**	**Raw**	**Scale**
Double vision on lateral gaze Right or left (circle one), secs	61	11-60	1-10	Spontaneous		
Ptosis (upward gaze)	61	11-60	1-10	Spontaneous		
Facial muscles	Normal lid closure	Complete, weak, some resistance	Complete, without resistance	Incomplete		
Swallowing 4 oz water (1/2 cup)	Normal	Minimal coughing or throat clearing	Severe coughing/choking or nasal regurgitation	Cannot swallow (test not attempted)		
Speech after counting aloud from 1 to 50 (onset of dysarthria)	None at 50	Dysarthria at 30-49	Dysarthria at 10-29	Dysarthria at 9		
Right arm outstretched (90 degrees sitting), seconds	240	90-239	10-89	0-9		
Left arm outstretched (90 degrees sitting), seconds	240	90-239	10-89	0-9		
Forced Vital Capacity	≥ 80	65-79	50-64	<50		
Rt- hand grip, kg Men Women	 ≥ 45 ≥ 30	 15-44 10-29	 5-14 5-9	 0-4 0-4		
Lt- hand grip, kg Men Women	 ≥ 35 ≥ 25	 15-34 10-24	 5-14 5-9	 0-4 0-4		
Head lifted (45 degrees supine seconds	120	30-119	1-29	0		
Right leg outstretched (45 degrees supine), seconds	100	31-99	1-30	0		
Left leg outstretched (45 degrees supine), seconds	100	31-99	1-30	0		
				TOTAL QMG SCORE :		

The actual forms will be provided to the sites and should be used for assessment.

Appendix 8
Myasthenia Gravis Composite Scale

Ptosis, upward gaze (physician examination)	>45 seconds=0	11–45 seconds=1	1–10 seconds=2	Immediate=3
Double vision on lateral gaze, left or right (physician examination)	>45 seconds=0	11–45 seconds=1	1–10 seconds=3	Immediate=4
Eye closure (physician examination)	Normal=0	Mild weakness (can be forced open with effort) =0	Moderate weakness (can be forced open easily) =1	Severe weakness (unable to keep eyes closed) =2
Talking (patient history)	Normal=0	Intermittent slurring or nasal speech =2	Constant slurring or nasal but can be understood =4	Difficult to understand speech =6
Chewing (patient history)	Normal=0	Fatigue with solid food=2	Fatigue with soft food=4	Gastric tube=6
Swallowing (patient history)	Normal=0	Rare episode of choking or trouble swallowing=2	Frequent trouble swallowing, e.g., necessitating changes in diet =5	Gastric tube=6
Breathing (thought to be caused by MG)	Normal=0	Shortness of breath with exertion =2	Shortness of breath at rest =4	Ventilator dependence=9
Neck flexion or extension (weakest) (physician examination)	Normal=0	Mild weakness=1	Moderate weakness (i.e., ~50% weak, ±15%=3[a]	Severe weakness=4

Shoulder abduction (physician examination)	Normal = 0	Mild weakness = 2	Moderate weakness (i.e., ~50% weak, ±15% = 4[a]	Severe weakness = 5
Hip flexion (physician examination)	Normal = 0	Mild weakness = 2	Moderate weakness (i.e., ~50% weak, ±15% = 4[a]	Severe weakness = 5
[a] Moderate weakness for neck and limb items should be construed as weakness that equals roughly 50% ± 15% of expected normal strength. Any weakness milder than that would be mild and any weakness more severe than that would be classified as severe				
				Total MGC Score

The actual forms will be provided to the sites and should be used for assessment.

REFERENCE

Burns T, Conaway M, Sanders, D. The MG Composite: A valid and reliable outcome measure for myasthenia gravis. Neurology 2010;74:1434–40.

Appendix 9
Myasthenia Gravis Quality of Life 15 (revised) (MG-QOL 15r)

Please indicate how true each statement has been (over the past few weeks).	Not at all 0	Somewhat 1	Very much 2
1. I am frustrated by my MG			
2. I have trouble with my eyes because of my MG (e.g. double vision)			
3. I have trouble eating because of MG			
4. I have limited my social activity because of my MG			
5. My MG limits my ability to enjoy hobbies and fun activities			
6. I have trouble meeting the needs of my family because of my MG			
7. I have to make plans around my MG			
8. I am bothered by limitations in performing my work (include work at home) because of my MG.			
9. I have difficulty speaking due to MG			
10. I have lost some personal independence because of my MG (e.g. driving, shopping, running errands)			
11. I am depressed about my MG			
12. I have trouble walking due to MG			
13. I have trouble getting around public places because of my MG			
14. I feel overwhelmed by my MG			
15. I have trouble performing my personal grooming needs due to MG			

Total MGOOL-R score

The actual forms will be provided to the sites and should be used for assessment.

Appendix 10
EuroQoL EQ-5D-5L

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

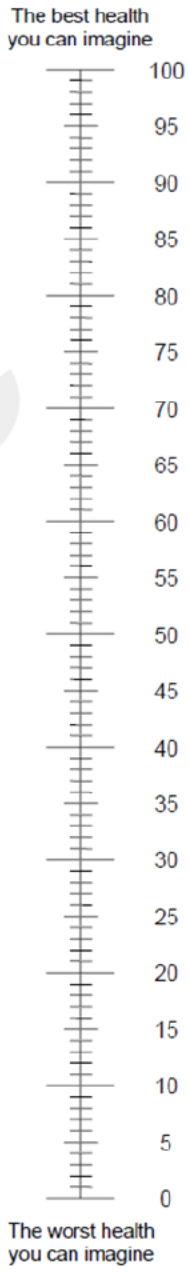
ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

2

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



The actual forms will be provided to the sites and should be used for assessment.

Appendix 11
Columbia-Suicide Severity Rating Scale (C-SSRS) at Baseline

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@childpsych.columbia.edu

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	Lifetime: Time He/She Felt Most Suicidal
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. ***Most Severe Ideation:*** ____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain. (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____

Version 1/14/09

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is *any* intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm,*** just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

The actual forms will be provided to the sites and should be used for assessment.

Appendix 12
Columbia-Suicide Severity Rating Scale (C-SSRS) since Last Visit

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	Since Last Visit
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** ____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____

Version 1/14/09

Appendix 12: C-SSRS since Last Visit (cont.)

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Since Last Visit
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	Yes ☐ No ☐ Total # of Attempts _____ Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐
Suicide:	Yes ☐ No ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

The actual forms will be provided to the sites and should be used for assessment.

Appendix 13
Neuro-QOL Item Bank v1.0–Fatigue Short Form

Fatigue – Short Form

Please respond to each question or statement by marking one box per row.

	In the past 7 days…	Never	Rarely	Sometimes	Often	Always
NQFTG13	I felt exhausted……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTG11	I felt that I had no energy……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTG15	I felt fatigued……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTG06	I was too tired to do my household chores.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTG07	I was too tired to leave the house……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTG10	I was frustrated by being too tired to do the things I wanted to do……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTG14	I felt tired……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQFTG02	I had to limit my social activity because I was tired……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

The actual forms will be provided to the sites and should be used for assessment.

Appendix 14
Myasthenia Gravis Foundation of America Clinical Classification

Class I: Any ocular muscle weakness; may have weakness of eye closure. All other muscle strength is normal.

Class II: Mild weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.

A. IIa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
B. IIb. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.

Class III: Moderate weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.

A. IIIa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
B. IIIb. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.

Class IV: Severe weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity.

A. IVa. Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
B. IVb. Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.

Class V: Defined as intubation, with or without mechanical ventilation, except when employed during routine postoperative management. The use of a feeding tube without intubation places the patient in class IVb.

Source: myasthenia.org.

Appendix 15
Investigational Medicinal Product and Auxiliary Medicinal Products Designations (for Use in European Economic Area)

Table 1 *Investigational, Authorized Auxiliary, and Unauthorized Auxiliary Medicinal Product Designations for European Economic Area*

Product Name	*IMP/AxMP Designation*	*Marketing Authorization Status in EEA*	*Used within Marketing Authorization*
Satralizumab (RO5333787)	*IMP (test product)*	*Authorized*	*No* [a]
Placebo (satralizumab RO5333787)	*IMP (placebo)*	*Unauthorized*	*Not applicable*
Azathioprine	*AxMP (background therapy)*	*Authorized*	*Yes* [b]
Mycophenolate mofetil	*AxMP* [c] *(background therapy)*	*Authorized*	*No*
Cyclosporin A	*AxMP* [c] *(background therapy)*	*Authorized*	*No*
Tacrolimus	*AxMP* [c] *(background therapy)*	*Authorized*	*No*
Oral glucocorticoids	*AxMP (background therapy)*	*Authorized*	*Yes* [b]
Pyridostigmine	*AxMP (background therapy)*	*Authorized*	*Yes* [b]
Neostigmine	*AxMP (background therapy)*	*Authorized*	*Yes* [b]
Ambenonium	*AxMP (background therapy)*	*Authorized*	*Yes* [b]
Intravenous immunoglobulin	*AxMP* [c] *(rescue medication)*	*Authorized*	*No*
Methylprednisolone (IV)	*AxMP (rescue medication)*	*Authorized*	*Yes* [b]

AxMP = auxiliary medicinal product; EEA = European Economic Area; IMP = investigational medicinal product;

[a] *Satralizumab is approved as a monotherapy or in combination with immunosuppressive therapy (IST) for the treatment of neuromyelitis optica spectrum disorders (NMOSD) in adult and adolescent patients from 12 years of age who are anti-aquaporin-4 IgG (AQP4-IgG) seropositive*

[b] *Azathioprine, oral glucocorticoids, pyridostigmine, neostigmine, ambenoniumand Methylprednisolone (IV) are approved for the treatment of myasthenia gravis in the EEA, and thereforeare considered authorized AxMPs*

[c] *Mycophenolate mofetil, cyclosporin A, tacrolimus and itravenous immunoglobulin are classified as authorized AxMPs based on the International Consensus Guideline for management of Myasthenia Gravis (Neurology 2016) even though not authorized in EEA for this indication*

Signature Page for Protocol - WN42636 - ENSPRYNG - v5 - Global/Core - Published
System identifier: RIM-CLIN-496147

Approval Task	[redacted] Company Signatory 21-Jul-2023 10:58:13 GMT+0000